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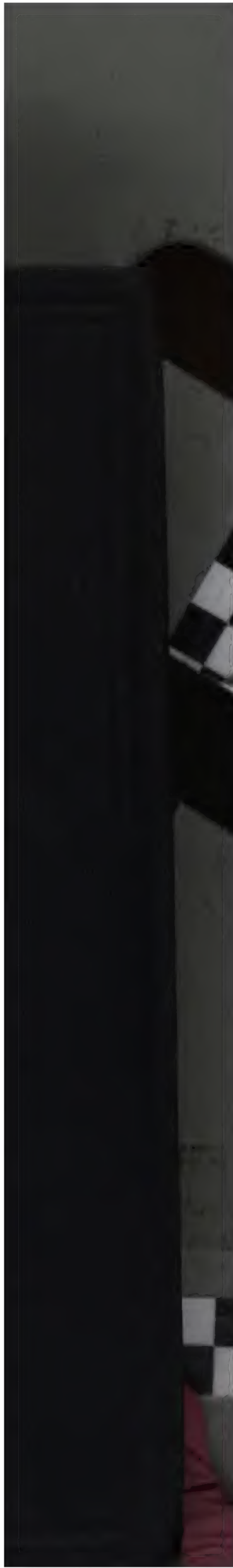
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Dr. J.M. Wolfsohn

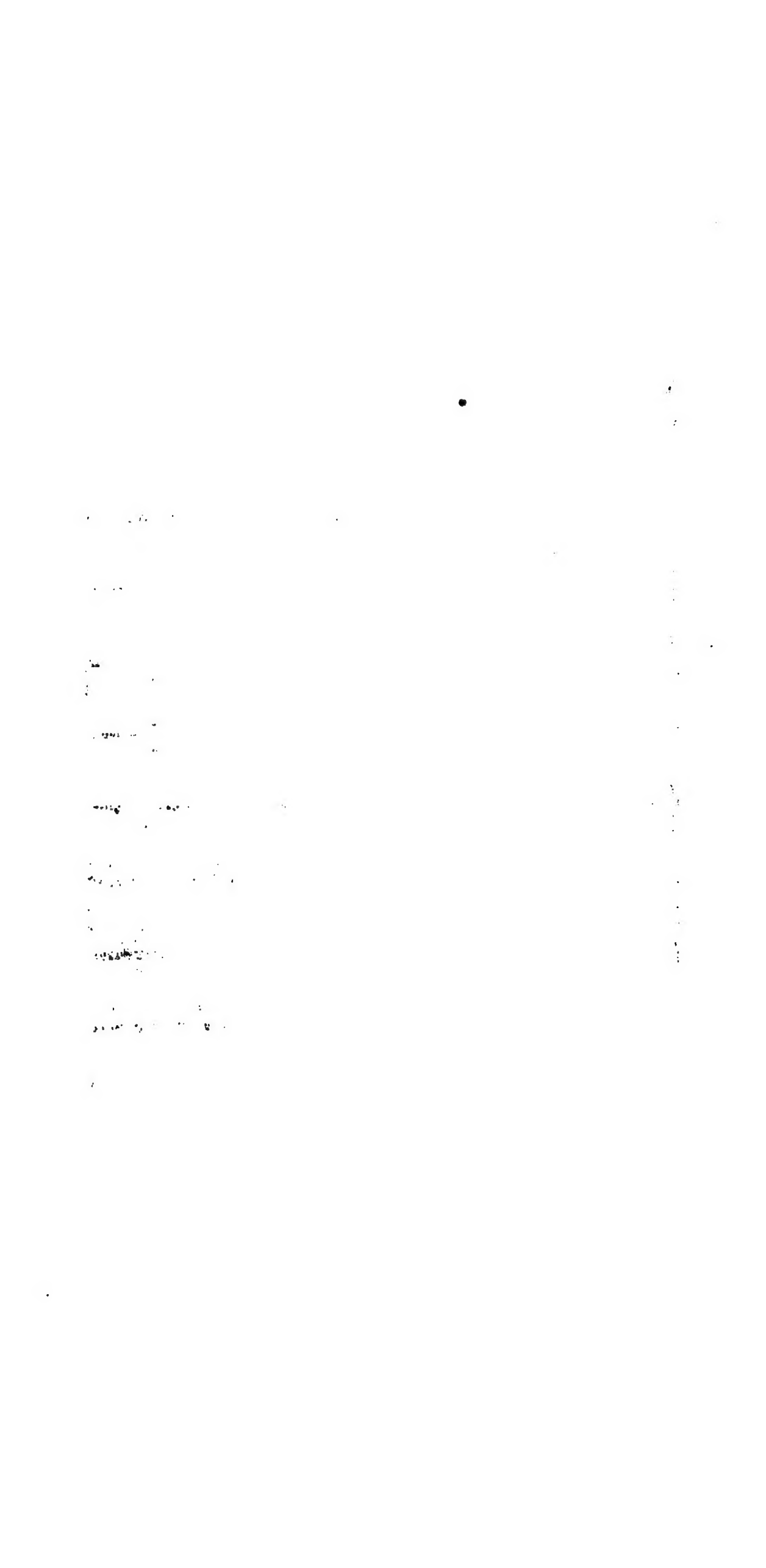
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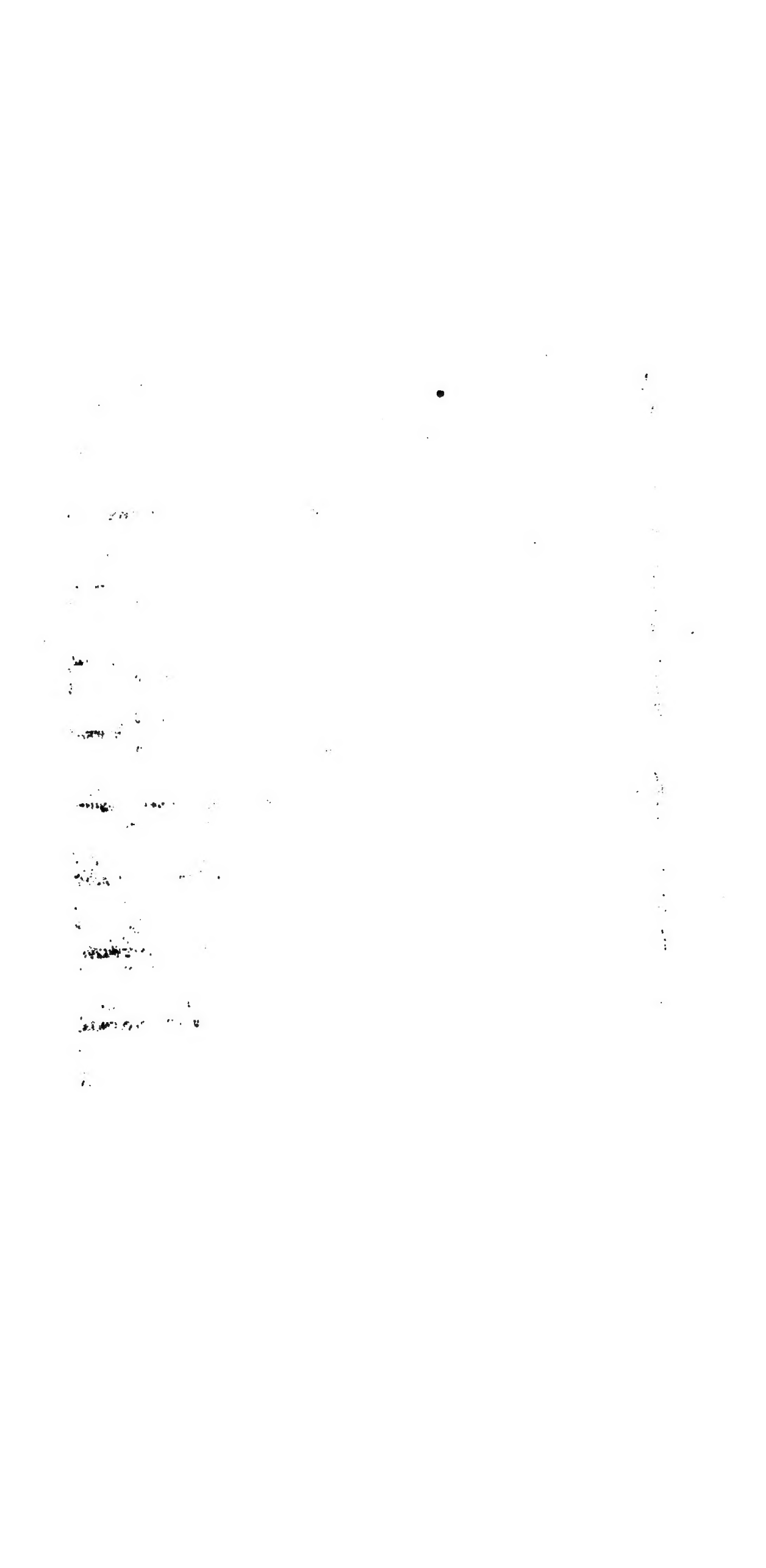


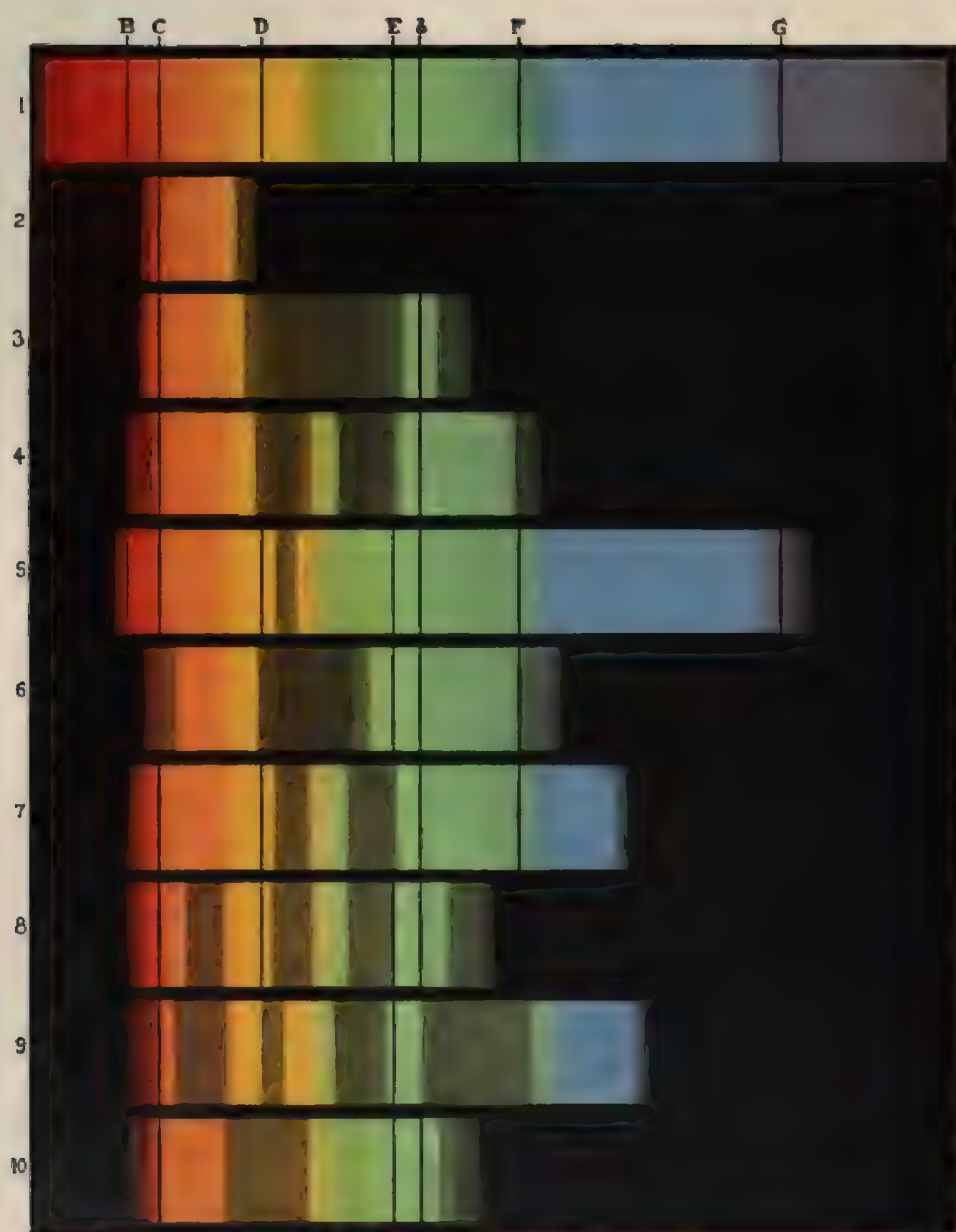












1. Solar spectrum with Fraunhofer lines. 2. Absorption spectrum of a concentrated solution of oxyhemoglobin, all the light is absorbed except in the red and orange. 3. Absorption spectrum of a less concentrated solution of oxyhemoglobin. 4. Absorption spectrum of a dilute solution of oxyhemoglobin, showing the two characteristic bands. 5. Absorption spectrum of a very dilute solution of oxyhemoglobin, showing only the  $\alpha$ -band. 6. Absorption spectrum of a dilute solution of reduced hemoglobin, showing the characteristic single band (to be compared with spectrum 4). 7. Absorption spectrum of a dilute solution of carbon monoxide hemoglobin (to be compared with spectrum 4). 8. Absorption spectrum of methemoglobin. 9. Absorption spectrum of acid hematin alcoholic solutions. 10. Absorption spectrum of alkaline hematin alcoholic solutions—modified from MacMunn, *The Spectroscope in Medicine*.

AN AMERICAN TEXT-BOOK  
OF  
**PHYSIOLOGY**

EDITED BY  
HENRY P. BOWDITCH, M.D., *Harvard Medical School*  
JOHN G. CUSTIS, M.D., *Harvard Medical School*  
HENRY H. DONALDSON, Ph.D., *Harvard University*  
W. H. HOWELL, Ph.D., M.D., *Harvard Medical School*  
ERIC S. LEE, Ph.D., *Harvard University*

EDITED BY  
WILLIAM H. HOWELL, Ph.D.

*Physiology of the Fishes, Frogs, Reptiles, Birds, and Mammals*

*SECOND EDITION, REVISED*

VOL. I

BY  
ROBERT M. WOOD AND GEORGE S. WOOD,  
Jr., *Harvard Medical School*  
AND  
J. H. HEDGECOCK, *Harvard University*  
CHEMISTS

PHILADELPHIA  
W. B. SAUNDERS & COMPANY

1900

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Color calibration chart showing a grid of color patches and grayscale steps. The chart is used for ensuring color accuracy in digital imaging and printing. The patches are arranged in a grid, with the top row showing a range of colors and the bottom row showing a range of grayscale values.

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BY

HENRY P. BOWDITCH, M.D.	WARREN P. LOMBARD, M.D.
JOHN G. CURTIS, M.D.	GRAHAM LUSK, PH.D., F.R.S. (EDIN.)
HENRY H. DONALDSON, PH.D.	W. T. PORTER, M.D.
W. H. HOWELL, PH.D., M.D.	EDWARD T. REICHERT, M.D.
FREDERIC S. LEE, PH.D.	HENRY SEWALL, PH.D., M.D.

EDITED BY

**WILLIAM H. HOWELL, PH.D., M.D.**

*Professor of Physiology in the Johns Hopkins University, Baltimore, Md.*

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AND NUTRITION; RESPIRATION AND ANIMAL HEAT;  
CHEMISTRY OF THE BODY

PHILADELPHIA

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## CONTRIBUTORS TO VOL. I.

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**JOHN G. CURTIS, M.D.,**

Professor of Physiology in Columbia University (College of Physicians and Surgeons).

**W. H. HOWELL, PH. D., M. D.,**

Professor of Physiology in the Johns Hopkins University.

**GRAHAM LUSK, PH. D., F. R. S. (EDIN.),**

Professor of Physiology in the University and Bellevue Hospital Medical College, New York.

**W. T. PORTER, M. D.,**

Associate Professor of Physiology in the Harvard Medical School.

**EDWARD T. REICHERT, M. D.,**

Professor of Physiology in the University of Pennsylvania.

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## PREFACE TO THE SECOND EDITION.

ADVANTAGE has been taken of the necessity of issuing a second edition of the American Text-Book of Physiology to alter somewhat its general arrangement. The book has proved to be successful, and for the most part has met only with kindly and encouraging criticisms from those who have made use of it. Many teachers, however, have suggested that the size of the book, when issued in a single volume, has constituted to some extent an inconvenience when regarded from the standpoint of a student's text-book that may be needed daily for consultation in the lecture-room or the laboratory. It has been thought best, therefore, to issue the present edition in two volumes, with the hope that the book may thereby be made more serviceable to those for whose aid it was especially written.

This change in the appearance of the book has necessitated also some alteration in the arrangement of the sections, the part upon the Physiology of Nerve and Muscle being transferred to the second volume, so as to bring it into its natural relations with the Physiology of the Central Nervous System.

The actual amount of material in the book remains substantially the same as in the first edition, although, naturally, very many changes have been made. Even in the short time that has elapsed since the appearance of the first edition there has been much progress in physiology, as the result of the constant activity of experimenters in this and the related sciences in all parts of the world, and an effort has been made by the various contributors to keep pace with this progress. Statements and theories that have been shown to be wrong or improbable have been eliminated, and the new facts discovered and the newer points of view have been incorporated so far as possible. Such changes are found scattered throughout the book.

The only distinctly new matter that can be referred to specifically is found in the section upon the Central Nervous System, and in a short section upon the modern ideas and nomenclature of physical chemistry, with reference especially to the processes of osmosis and diffusion. The section dealing with the Central Nervous System has been recast in large part, with the intention of making it more suitable to the actual needs of medical students; while a brief presentation of some of the elementary conceptions of physical chemistry seems to be necessary at the present time, owing to the large part that these views are taking in current discussions in physiological and medical literature.

The index has been revised thoroughly and considerably amplified, a table of contents has been added to each volume, and numerous new figures have been introduced.

AUGUST, 1900.

## PREFACE.

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THE collaboration of several teachers in the preparation of an elementary text-book of physiology is unusual, the almost invariable rule heretofore having been for a single author to write the entire book. It does not seem desirable to attempt a discussion of the relative merits and demerits of the two plans, since the method of collaboration is untried in the teaching of physiology, and there is therefore no basis for a satisfactory comparison. It is a fact, however, that many teachers of physiology in this country have not been altogether satisfied with the text-books at their disposal. Some of the more successful older books have not kept pace with the rapid changes in modern physiology, while few, if any, of the newer books have been uniformly satisfactory in their treatment of all parts of this many-sided science. Indeed, the literature of experimental physiology is so great that it would seem to be almost impossible for any one teacher to keep thoroughly informed on all topics. This fact undoubtedly accounts for some of the defects of our present text-books, and it is hoped that one of the advantages derived from the collaboration method is that, owing to the less voluminous literature to be consulted, each author has been enabled to base his elementary account upon a comprehensive knowledge of the part of the subject assigned to him. Those who are acquainted with the difficulty of making a satisfactory elementary presentation of the complex and oftentimes unsettled questions of physiology must agree that authoritative statements and generalizations, such as are frequently necessary in text-books if they are to leave any impression at all upon the student, are usually trustworthy in proportion to the fulness of information possessed by the writer.

Perhaps the most important advantage which may be expected to follow the use of the collaboration method is that the student gains thereby the point of view of a number of teachers. In a measure he reaps the same benefit as would be obtained by following courses of instruction under different teachers. The different standpoints assumed, and the differences in emphasis laid upon the various lines of procedure, chemical, physical, and anatomical, should give the student a better insight into the methods of the science as it exists

to-day. A similar advantage may be expected to follow the inevitable overlapping of the topics assigned to the various contributors, since this has led in many cases to a treatment of the same subject by several writers, who have approached the matter under discussion from slightly varying standpoints, and in a few instances have arrived at slightly different conclusions. In this last respect the book reflects more faithfully perhaps than if written by a single author the legitimate differences of opinion which are held by physiologists at present with regard to certain questions, and in so far it fulfils more perfectly its object of presenting in an unprejudiced way the existing state of our knowledge. It is hoped, therefore, that the diversity in method of treatment, which at first sight might seem to be disadvantageous, will prove to be the most attractive feature of the book.

In the preparation of the book it has been assumed that the student has previously obtained some knowledge of gross and microscopic anatomy, or is taking courses in these subjects concurrently with his physiology. For this reason no systematic attempt has been made to present details of histology or anatomy, but each author has been left free to avail himself of material of this kind according as he felt the necessity for it in developing the physiological side.

In response to a general desire on the part of the contributors, references to literature have been given in the book. Some of the authors have used these freely, even to the point of giving a fairly complete bibliography of the subject, while others have preferred to employ them only occasionally, where the facts cited are recent or are noteworthy because of their importance or historical interest. References of this character are not usually found in elementary text books, so that a brief word of explanation seems desirable. It has not been supposed that the student will necessarily look up the references or commit to memory the names of the authorities quoted, although it is possible, of course, that individual students may be led to refer occasionally to original sources, and thereby acquire a truer knowledge of the subject. The main result hoped for, however, is a healthful pedagogical influence. It is too often the case that the student of medicine, or indeed the graduate in medicine, regards his text-book as a final authority, losing sight of the fact that such books are mainly compilations from the works of various investigators, and that in all matters in dispute in physiology the final decision must be made, so far as possible, upon the evidence furnished by experimental work. To enforce this latter idea and to indicate the character and source of the great literature from which the material of the text-book is obtained have been the main reasons for the adoption of the reference system. It is hoped also that the

book will be found useful to many practitioners of medicine who may wish to keep themselves in touch with the development of modern physiology. For this class of readers references to literature are not only valuable, but frequently essential, since the limits of a text-book forbid an exhaustive discussion of many points of interest concerning which fuller information may be desired.

The numerous additions which are constantly being made to the literature of physiology and the closely related sciences make it a matter of difficulty to escape errors of statement in any elementary treatment of the subject. It cannot be hoped that this book will be found entirely free from defects of this character, but an earnest effort has been made to render it a reliable repository of the important facts and principles of physiology, and, moreover, to embody in it, so far as possible, the recent discoveries and tendencies which have so characterized the history of this science within the last few years.



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M. Abrams.

# AN AMERICAN TEXT-BOOK OF PHYSIOLOGY.

## I. INTRODUCTION.

THE term "physiology" is, in an etymological sense, synonymous with "natural philosophy," and occasionally the word is used with this significance even at the present day.<sup>1</sup> By common usage, however, the term is restricted to the living side of nature, and is meant to include the sum of our knowledge concerning the properties of living matter. The active substance of which living things are composed is supposed to be fundamentally alike in structure in all cases, and is commonly designated as protoplasm (*πρῶτος*, first, and *πλάσμα*, anything formed). It is usually stated that this word was first introduced into biological literature by the botanist Von Mohl to designate the granular semi-liquid contents of the plant-cell. It seems, however, that priority in the use of the word belongs to the physiologist Purkinje (1840), who employed it to describe the material from which the young animal embryo is constructed.<sup>2</sup> In recent years the term has been applied indifferently to the soft material constituting the substance of either animal or plant-cells. The word must not be understood to mean a substance of a definite chemical nature or of an invariable morphological structure; it is applied to any part of a cell that shows the properties of life, and is therefore only a convenient abbreviation for the phrase "mass of living matter."

Living things fall into two great groups, animals and plants, and corresponding to this there is a natural separation of physiology into two sciences, one dealing with the phenomena of animal life, the other with plant life. In what follows in this introductory section the former of these two divisions is chiefly considered, for although the most fundamental laws of physiology are, without doubt, equally applicable to animal and vegetable protoplasm, nevertheless the structure as well as the properties of the two forms of matter are in some respects noticeably different, particularly in the higher types of organisms in each group. The most striking contrast, perhaps, is found in the fact that plants exhibit a lesser degree of specialization in form and function and

<sup>1</sup> See *Mineral Physiology and Phytography*, T. Sterry Hunt, 1886.

<sup>2</sup> O. Hertwig: *Die Zelle und die Gewebe*, 1893.



a much greater power of assimilation. Owing to this latter property the plant-cell is able, with the aid of solar energy, to construct its protoplasm from very simple forms of inorganic matter, such as water, carbon dioxide, and inorganic salts. In this way energy is stored within the vegetable cell in the substance of complex organic compounds. Animal protoplasm, on the contrary, has comparatively feeble synthetic properties; it is characterized chiefly by its destructive power. In the long run, animals obtain their food from the plant kingdom, and the animal cell is able to dissociate or oxidize the complex material of vegetable protoplasm and thus liberate the potential energy contained therein, the energy taking the form mainly of heat and muscular work. We must suppose that there is a general resemblance in the ultimate structure of animal and vegetable living matter to which the fundamental similarity in properties is due, but at the same time there must be also some common difference in internal structure between the two, and it is fair to assume that the divergent properties exhibited by the two great groups of living things are a direct outcome of this structural dissimilarity; to make use of a figure of speech employed by Bichat, plants and animals are cast in different moulds.

It is difficult, if not impossible, to settle upon any one property that absolutely shall distinguish living from dead matter. Nutrition, that is, the power of converting dead food material into living substance, and reproduction, that is, the power of each organism to perpetuate its kind by the formation of new individuals, are probably the most fundamental characteristics of living things; but in some of the specialized tissues of higher animals the power of reproduction, so far as this means mere multiplication by cell-division, seems to be lost, as, for example, in the case of the nerve-cells in the central nervous system or of the matured ovum itself before it is fertilized by the spermatozoon. Nevertheless these cellular units are indisputably living matter, and continue to exhibit the power of nutrition as well as other properties characteristic of the living state. It is possible also that the power of nutrition may, under certain conditions, be held in abeyance, temporarily at least, although it is certain that a permanent loss of this property is incompatible with the retention of the living condition.

It is frequently said that the most general property of living matter is its irritability. The precise meaning of the term vital irritability is hard to define. The word implies the capability of reacting to a stimulus and usually also the assumption that in the reaction some of the inner potential energy of the living material is liberated, so that the energy of the response is many times greater, it may be, than the energy of the stimulus. This last idea is illustrated by the case of a contracting muscle, in which the stimulus acts as a liberating force causing chemical decompositions of the substance of the muscle with the liberation of a comparatively large amount of energy, chiefly in the form of heat or of heat and work. It may be remarked in passing, however, that we are not justified at present in assuming that a similar liberation of stored energy takes place in all irritable tissues. In the case of nerve-fibres, for instance, we have a typically irritable tissue which responds readily to

external stimuli, but as yet it has not been possible to show that the formation or conduction of a nerve impulse is accompanied by or dependent upon a liberation of so-called potential chemical energy. The nature of the response of irritable living matter is found to vary with the character of the tissue or organism on the one hand, and, so far as intensity goes at least, with the nature of the stimulus on the other. Response of a definite character to appropriate external stimulation may be observed frequently enough in dead matter, and in some cases the nature of the reaction simulates closely some of those displayed by living things. For instance, a dead catgut string may be made to shorten after the manner of a muscular contraction by the appropriate application of heat, or a mass of gunpowder may be exploded by the action of a small spark and give rise to a great liberation of energy that had previously existed in potential form within its molecules. As regards any piece of matter we can only say that it exhibits vital irritability when the reaction or response it gives upon stimulation is one characteristic of living matter in general or of the particular kind of living matter under observation; thus, a muscle-fibre contracts, a nerve-fibre conducts, a gland-cell secretes, an entire organism moves or in some way adjusts itself more perfectly to its environment. Considered from this standpoint, irritability means only the exhibition of one or more of the peculiar properties of living matter and cannot be used to designate a property in itself distinctive of living structure; the term, in fact, comprises nothing more specific or characteristic than is implied in the more general phrase vitality. When an amoeba dies it is no longer irritable, that is, its substance no longer assimilates when stimulated by the presence of appropriate food, its conductivity and contractility disappear so that mechanical irritation no longer causes the protrusion or retraction of pseudopodia—no form of stimulation, in fact, is capable of calling forth any of the recognized properties of living matter. To ascertain, therefore, whether or not a given piece of matter possesses vital irritability we must first become acquainted with the fundamental properties of living matter in order to recognize the response, if any, to the form of stimulation used.

Nutrition or assimilation, in a wide sense of the word, has already been referred to as probably the most universal and characteristic of these properties. By this term we designate that series of changes through which dead matter is received into the structure of living substance. The term in its broadest sense may be used to cover the subsidiary processes of digestion, respiration, absorption, and excretion through which food material and oxygen are prepared for the activity of the living molecules, and the waste products of activity are removed from the organism, as well as the actual conversion of dead material into living protoplasm. This last act, which is presumably a synthetic process effected under the influence of living matter, is especially designated as anabolism or as assimilation in a narrower sense of the word as opposed to disassimilation. By disassimilation or katabolism we mean those changes leading to the destruction of the complex substance of the living molecules, or of the food material in contact with these molecules.



As was said before, animal protoplasm is pre-eminently katabolic, and the evidence of its katabolism is found in the waste products, such as  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ , and urea, which are given off from animal organisms. Assimilation and disassimilation, or anabolism and katabolism, go hand in hand, and together constitute an ever-recurring cycle of activity that persists as long as the material retains its living structure, and is designated under the name metabolism. In most forms of living matter metabolism is in some way self-limited, so that gradually it becomes less perfect, old age comes on, and finally death ensues. It has been asserted that originally the metabolic activity of protoplasm was self-perpetuating—that, barring accident, the cycle of changes would go on forever. Resting upon this assumption it has been suggested by Weissmann that the protoplasm of the reproductive elements still retains this primitive and perfect metabolism and thus provides for the continuity of life. The speculations bearing upon this point will be discussed in more detail in the section on Reproduction.

Reproduction in some form is also practically a universal property of living matter. The unit of structure among living organisms is the cell. Under proper conditions of nourishment the cell may undergo separation into two daughter cells. In some cases the separation takes place by a simple act of fission, in other cases the division is indirect and involves a number of interesting changes in the structure of the nucleus and the protoplasm of the body of the cell. In the latter case the process is spoken of as karyokinesis or mitosis. This act of division was supposed formerly to be under the control of the nucleus of the cell, but modern histology has shown that in karyokinetic division the process, in many cases at least, is initiated by a special structure to which the name centrosome has been given. The many-celled animals arise by successive divisions of a primitive cell, the ovum, and in the higher forms of life the ovum requires to be fertilized by union with a spermatozoon before cell-division becomes possible. The sperm-cell acts as a stimulus to the egg-cell (see section on Reproduction), and rapid cell-division is the result of their union. It must be noted also that the term reproduction includes the power of hereditary transmission. The daughter-cells are similar in form to the parent-cell, and the organism produced from a fertilized ovum is substantially a facsimile of the parent forms. Living matter, therefore, not only exhibits the power of separating off other units of living matter, but of transmitting to its progeny its own peculiar internal structure and properties.

Contractility and conductivity are properties exhibited in one form or another in all animal organisms, and we must concede that they are to be counted among the primitive properties of protoplasm. The power of contracting or shortening is, in fact, one of the commonly recognized features of a living thing. It is generally present in the simplest forms of animal as well as vegetable life, although in the more specialized forms it is found most highly developed in animal organisms. The opinion seems to be general among physiologists that wherever this property is exhibited, whether in the

formation of the pseudopodia of an amoeba or white blood-corpuscle, or in the vibratile movements of ciliary structures, or in the powerful contractions of voluntary muscle, the underlying mechanism by which the shortening is produced is essentially the same throughout. However general the property may be, it cannot be considered as absolutely characteristic of living structure. As was mentioned before, Engelmann<sup>1</sup> has been able to show that a dead catgut string when surrounded by water of a certain temperature and exposed to a sudden additional rise of temperature will contract or shorten in a manner closely analogous to the contraction of ordinary muscular tissue, and it is not at all impossible that the molecular processes involved in the shortening of the catgut string and the muscle-fibre may be essentially the same.

That conductivity is also a fundamental property of primitive protoplasmic structure seems to be assured by the reactions which the simple motile forms of life exhibit when exposed to external stimulation. An irritation applied to one point of a protoplasmic mass may produce a reaction involving other parts, or indeed the whole extent of the organism. The phenomenon is most clearly exhibited in the more specialized animals possessing a distinct nervous system. In these forms a stimulus applied to one organ, as for instance light acting upon the eye, may be followed by a reaction involving quite distant organs, such as the muscles of the extremities, and we know that in these cases the irritation has been conducted from one organ to the other by means of the nervous tissues. But here also we have a property that is widely exhibited in inanimate nature. The conduction of heat, electricity, and other forms of energy is familiar to every one. While it is quite possible that conduction through the substance of living protoplasm is something *sui generis*, and does not find a strict parallel in dead structures, yet it must be admitted that it is conceivable that the molecular processes involved in nerve conduction may be essentially the same as prevail in the conduction of heat through a solid body, or in the conduction of a wave of pressure through a liquid mass. At present we know nothing definite as to the exact nature of vital conduction, and can therefore affirm nothing.

The four great properties enumerated, namely, nutrition or assimilation (including digestion, secretion, absorption, excretion, anabolism, and katabolism), reproduction, conduction, and contractility, form the important features which we may recognize in all living things and which we make use of in distinguishing between dead and living matter. A fifth property perhaps should be added, that of sensibility or sensation, but concerning this property as a general accompaniment of living structure our knowledge is extremely imperfect; something more as to the difficulties connected with this subject will be said presently. The four fundamental properties mentioned are all exhibited in some degree in the simplest forms of life, such as the protozoa. In the more highly organized animals, however, we find that specialization of function prevails. Hand in hand with the differentiation in form that is displayed in the structure of the constituent tissues there goes a specialization

<sup>1</sup> *Ueber den Ursprung der Muskelkraft*, Leipzig, 1893.



in certain properties with a corresponding enlargement of other properties. The outcome of which is that different parts of the same protoplasmic mass, by power of conductivity, are more or less differentiated by a highly developed power of conductivity, and so on. Thus in the simple unicellular forms of animal life the fundamental properties are all exhibited equally extended within the compass of a single mass or cell. In the higher animals we have in each cell a vast complexity of cells organized into tissues each of which possesses some distinctive property. This specialization of function is almost exclusively in the physiological domain of life. The beginning of this process may be recognized in the cell itself. The whole cell is unity in organism of some complexity as compared with a simple mass of undifferentiated protoplasm. The protoplasm of the nucleus, particularly of that internal in the nucleus which is designated as chromatin, is differentiated, both histologically and physiologically, from the protoplasm of the rest of the cell, the so-called cytoplasm. The chromatin material in the resting cell is arranged usually in a network, but during the act of division it separates into a number of rods or filaments known as chromosomes. In the ovum there are good reasons for believing that the power of transmitting hereditary characteristics is dependent upon the structure of these chromosomes. The nucleus, moreover, controls in some way the metabolism of the entire cell, for it has been shown, in some cells at least, that a non-nucleated piece of the cytoplasm is not only deprived of the power of reproduction, but has also such limited powers of nutrition that it quickly undergoes disintegration. On the other hand contractility and conductivity, and some of the functions connected with nutrition, such as digestion and excretion, seem often to be specialized in the cytoplasm. As a further example of differentiation in the cell itself the existence of the centrosome may be referred to. The centrosome is a body of very minute size that has been discovered in numerous kinds of cells. It is considered by many observers to be a permanent structure of the cell, lying either in the cytoplasm, or possibly in some cases within the boundaries of the nucleus. When present it seems to have some special function in connection with the movements of the chromosomes during the act of cell-division. In the many-celled animals the primitive properties of protoplasm become highly developed in consequence of this subdivision of function among the various tissues, and in many ways the most complex animals are, from a physiological standpoint, the simplest for purposes of study, since in them the various properties of living matter are not only exhibited more distinctly, but each is, as it were, concentrated in some one part of the organism, and therefore be investigated more directly. The various properties so clearly recognizable in the more complex animals are all actually or potentially present in the protoplasm of the simplest unicellular animals. In other words the direction of life is finite, but on the contrary reflect that in spite of the complexity of the properties as well as the

forms of the differentiated tissues throughout the animal kingdom are strikingly alike. Striated muscle, with the characteristic property of sharp and powerful contraction, is everywhere found; the central nervous system in the invertebrates is built upon the same type as in the highest mammals, and the variations met with in different animals are probably but varying degrees of perfection in the development of the innate possibility contained in primitive protoplasm. It is not too much to say, perhaps, that were we acquainted with the structure and chemistry of the ultimate units of living substance, the key to the possibilities of the evolution of form and function would be in our possession.

Most interesting suggestions have been made in recent years as to the essential molecular structure of living matter. These views are necessarily very incomplete and of a highly speculative character, and their correctness or incorrectness is at present beyond the range of experimental proof; nevertheless they are sufficiently interesting to warrant a brief statement of some of them, as they seem to show at least the trend of physiological thought.

Pflüger,<sup>1</sup> in a highly interesting paper upon the nature of the vital processes, calls attention to the great instability of living matter. He supposes that living substance consists of very complex and very unstable molecules of a proteid nature which, because of the active intra-molecular movement present, are continually dissociating or falling to pieces with the formation of simpler and more stable bodies such as water, carbon dioxide and urea, the act of dissociation giving rise to a liberation of energy. "The intra-molecular heat (movement) of the cell is its life." He suggests that in this living molecule the nitrogen is contained in the form of a cyanogen compound, and that the instability of the molecule depends chiefly upon this particular grouping. Moreover the power of the molecule to assimilate dead proteid and convert it to living proteid like itself he attributes to the existence of the cyanogen group. It is known that cyanogen compounds possess the property of polymerization, that is, of combining with similar molecules to form more complex molecules, and we may suppose that the molecules of dead proteid when brought into contact with the living molecules are combined with the latter by a process analogous to polymerization or condensation. By this means the stable structure of dead proteid is converted to the labile structure of living proteid, and the molecules of the latter increase in size and instability. When living substance dies its molecules undergo alteration and become incapable of exhibiting the usual properties of life. Pflüger suggests that the change may consist essentially in an absorption of water whereby the cyanogen grouping passes over into an ammonia grouping. Loew<sup>2</sup> assumes also that the difference between dead and living or active proteid lies chiefly in the fact that in the latter we have a very unstable or labile molecule in which the atoms are in active motion. The instability of the molecules he likewise attributes to

<sup>1</sup> *Archiv für die gesammte Physiologie*, 1875, Bd. 10, S. 251.

<sup>2</sup> *Ibid.*, 1880, Bd. 22; Loew and Bokorny *Die chemische Kraftquelle in lebenden Protoplasma*, München, 1882; Imperial Institute of Tokyo (College of Agriculture), 1894.



the existence of certain groupings of the atoms. Influenced in part by the power of living material to reduce alkaline silver solutions, he supposes that the specially important labile group in the molecule is the aldehyde radical  $-\text{C} \begin{smallmatrix} \text{=O} \\ \text{---H} \end{smallmatrix}$ . The nitrogen exists also in a labile amido-combination,  $-\text{NH}_2$ ,

and the active or living form of these two groups may be expressed by the formula  $\begin{smallmatrix} -\text{CH} - \text{NH}_2 \\ | \\ =\text{C} \end{smallmatrix} - \text{C} \begin{smallmatrix} \text{=O} \\ \text{---H} \end{smallmatrix}$ . If this grouping by chemical change became con-

verted to the grouping  $\begin{smallmatrix} -\text{CH} - \text{NH} \\ | \\ =\text{C} \end{smallmatrix} - \text{CHOH}$ , it would form a comparatively inert compound such as we have in dead proteid. Latham<sup>1</sup> proposes a theory which combines the ideas of Pflüger and of Loew. He suggests that the living molecule may be composed of a chain of cyan-alcohols united to a benzene nucleus. The cyan-alcohols are obtained by the union of an aldehyde with hydrocyanic acid; they contain, therefore, the labile-aldehyde grouping as well as the cyanogen nucleus to which Pflüger attributes such importance.

Actual investigation of the chemical structure of living matter can hardly be said to have made a beginning. The first step in this direction has been made in the study of the chemical structure of the group of proteids which have usually been considered as forming the most characteristic constituent of protoplasm. Proteids as we obtain them from the dead tissues and liquids of the body have proved to be very varied in properties and structure, so much so in fact that it is impossible to give a satisfactory definition of the group. Many of them can be obtained in a pure, even in a crystalline form, and their percentage composition can therefore be determined with ease. But the fundamental chemical structure that may be supposed to characterize the proteid group, and the changes in this structure producing the different varieties of proteids are matters as yet undetermined. Several promising efforts have been made to construct proteids synthetically, but the results obtained are at present incomplete. On the other hand, Kossel<sup>2</sup> has isolated from the spermatozoa of certain fishes a comparatively simple nitrogenous body of basic properties (protamine), which he regards as the simplest form of proteid and the essential core or nucleus characterizing the structure of the whole group. It is an interesting thought that in the heads of the spermatozoa with their complex possibilities of development and hereditary transmission, dependent as these properties must be upon the chemical structure of the germ protoplasm, there may be found the simplest form of proteid. Kossel's work, it may be noted, has not gone so far as to indicate the possible molecular structure of the protamines.

It has been assumed by many observers that the properties of living matter, as we recognize them, are not solely an outcome of the inner structure of the hypothetical living molecules. They believe that these latter units are

<sup>1</sup> *British Medical Journal*, 1886, p. 629.

<sup>2</sup> *Zeitschrift für physiol. Chem.*, 1898; xxv. 1899, xxvi.

fashioned into larger secondary units each of which is a definite aggregate of chemical molecules and possesses certain properties or reactions that depend upon the mode of arrangement. The idea is similar to that advanced by mineralogists to explain the structure of crystals. They suppose that the chemical molecules are arranged in larger or smaller groups to which the name "physical molecules" has been given. So in living protoplasm it may be that the smallest particles capable of exhibiting the essential properties of life are groups of ultimate molecules, in the chemical sense, having a definite arrangement and definite physical properties. These secondary units of structure have been designated by various names such as "physiological molecules,"<sup>1</sup> "somaules,"<sup>2</sup> micellæ,<sup>3</sup> etc. Many facts, especially from the side of plant physiology, teach us that the physical constitution of protoplasm is probably of great importance in understanding its reaction to its environment. Microscopic analysis is insufficient to reveal the existence or character of these "physiological molecules," but it has abundantly shown that protoplasm has always a certain physical construction and is not merely a structureless fluid or semi-fluid mass.

What has been said above may serve at least to indicate the prevalent physiological belief that the phenomena shown by living matter are in the main the result of the action of the known forms of energy through a substance of a complex and unstable structure which possesses, moreover, a physical organization responsible for some of the peculiarities exhibited. In other words, the phenomena of life are referred to the physical and chemical structure of protoplasm and may be explained under the general physical and chemical laws which control the processes of inanimate nature. Just as in the case of dead organic or inorganic substances we attempt to explain the differences in properties between two substances by reference to the difference in chemical and physical structure between the two, so with regard to living matter the peculiar differences in properties that separate them from dead matter, or for that matter the differences that distinguish one form of living matter from another, must eventually depend upon the nature of the underlying physical and chemical structure.

In the early part of this century many prominent physiologists were still so overwhelmed with the mysteriousness of life that they took refuge in the hypothesis of a vital force or principle of life. By this term was meant a something of an unknown nature that controlled all the phenomena exhibited by living things. Even ordinary chemical compounds of a so-called organic nature were supposed to be formed under the influence of this force, and it was thought could not be produced otherwise. The error of this latter view has been demonstrated conclusively within recent years: many of the substances formed by the processes of plant and animal life are now easily produced within the laboratory by comparatively simple synthetic methods.

<sup>1</sup> Meltzer: "Ueber die fundamentale Bedeutung der Erschütterung für die lebende Materie," *Zeitschrift für Biologie*, Bd. xxx., 1894.

<sup>2</sup> Foster: *Physiology* (Introduction).

<sup>3</sup> Nägeli: *Theorie der Gährung*, München, 1879.



By the distinguished labors of Emil Fischer<sup>1</sup> even the structure of carbohydrate bodies has been determined, and bodies belonging to this group have been synthetically constructed in the laboratory. Moreover, the work of Schützenberger, Grimaux, and Pickering gives promise that before long proteid bodies may be produced by similar methods. Physiologists have shown, furthermore, that the digestion that takes place in the stomach or intestine may be effected also in test-tubes, and at the present day probably no one doubts that in the act of digestion we have to deal only with a series of chemical reactions which in time will be understood as clearly as it is possible to comprehend any form of chemical activity. Indeed, the whole history of food in the body follows strictly the great physical laws of the conservation of matter and of energy which prevail outside the body. No one disputes the proposition that the material of growth and of excretion comes entirely from the food. It has been demonstrated that the measureable energy given off from the body is all contained potentially within the food that is eaten.<sup>2</sup> Living things, so far as can be determined, can only transform matter and energy; they cannot create or destroy them, and in this respect they are like inanimate objects. But, in spite of the triumphs that have followed the use of the experimental method in physiology, every one recognizes that our knowledge is as yet very incomplete. Many important manifestations of life cannot be explained by reference to any of the known facts or laws of physics and chemistry, and in some cases these phenomena are seemingly removed from the field of experimental investigations. As long as there is this residuum of mystery connected with any of the processes of life, it is but natural that there should be two points of view. Most physiologists believe that as our knowledge and skill increase these mysteries will be explained, or rather will be referred to the same great final mysteries of the action of matter and energy under definite laws, under which we now classify the phenomena of lifeless matter. Others, however, find the difficulties too great,—they perceive that the laws of physics and chemistry are not completely adequate at present to explain all the phenomena of life, and assume that they never will be. They suppose that there is something in activity in living matter which is not present in dead matter, and which for want of a better term may be designated as vital force or vital energy. However this may be, it seems evident that a doctrine of this kind stifles inquiry. Nothing is more certain than the fact that the great advances made in physiology during the last four decades are mainly owing to the abandonment of this idea of an unknown vital force and the determination on the part of experimenters to make the greatest possible use of the known laws of nature in explaining the phenomena of life. There is no reason to-day to suppose that we have exhausted the results to be obtained by the application of the methods of physics and chemistry to the study of living things, and as a matter of fact the great bulk of physiological research is proceeding along these lines. It is interesting, however, to stop

<sup>1</sup> *Die Chemie der Kohlenhydrate*, Berlin, 1894.

<sup>2</sup> Rubner: *Zeitschrift für Biologie*, Bd. xxx. S. 73, 1894.

for a moment to examine briefly some of the problems which as yet have escaped satisfactory solution by these methods.

The phenomena of secretion and absorption form important parts of the digestive processes in higher animals, and without doubt are exhibited in a minor degree in the unicellular types. In the higher animals the secretions may be collected and analyzed, and their composition may be compared with that of the lymph or blood from which they are derived. It has been found that secretions may contain entirely new substances not found at all in the blood, as for example the mucin of saliva or the ferments and HCl of gastric juice; or, on the other hand, that they may contain substances which, although present in the blood, are found in much greater percentage amounts in the secretion—as, for instance, is the case with the urea eliminated in the urine. In the latter case we have an instance of the peculiar, almost purposeful, elective action of gland-cells of which many other examples might be given. With regard to the new material present in the secretions, it finds a sufficient general explanation in the theory that it arises from a metabolism of the protoplasmic material of the gland-cell. It offers, therefore, a purely chemical problem which may and probably will be worked out satisfactorily for each secretion. The selective power of gland-cells for particular constituents of the blood is a more difficult question. We find no exact parallel for this kind of action in chemical literature, but there can be no reasonable doubt that the phenomenon is essentially a chemical or physical reaction involving the activity of some of the forms of energy with which the study of inanimate objects has already made us partially familiar. We may indulge the hope that the details of the reaction will be discovered by more complete chemical and microscopical study of the structure of these cells. If in the meantime the act of selection is spoken of as a vital phenomenon, it is not meant thereby that it is referred to the action of an unknown vital force, but only that it is a kind of action dependent upon the living structure of the cell-substance.

The act of absorption of digested products from the alimentary canal was for a time supposed to be explained completely by the laws of imbibition, diffusion, and osmosis. The epithelial lining and its basement membrane form a septum dividing the blood and lymph on the one side from the contents of the alimentary canal on the other. Inasmuch as the two liquids in question are of unequal composition with regard to certain constituents, a diffusion stream should be set up whereby the peptones, sugar, salts, etc. would pass from the liquid in the alimentary canal, where they exist in greater concentration, into the blood, where the concentration is less. Careful work of recent years has shown that the laws of diffusion and osmosis are not adequate to explain fully the absorption that actually occurs; a more detailed account of the difficulties met with may be found in the section on Digestion and Nutrition. It has become customary to speak of absorption as caused in part by the physical laws of diffusion and osmosis, and in part by the vital activity of the epithelial cells. It will be noticed that the vital property in this case is again an elective affinity for certain constituents similar to that which has been



referred to in discussing the act of secretion. The mere fact that the physical theory has proved so far to be insufficient is in itself no reason for abandoning all hope of a satisfactory explanation. Most physiologists probably believe that further experimental work will bring this phenomenon out of its obscurity and show that it is explicable in terms of known physical and chemical forces exerted through the peculiar substance of the absorptive cell.

The facts of heredity and consciousness offer difficulties of a much graver character. The function of reproduction is two-sided. In the first place there is an active multiplication of cells, beginning with the segmentation of the ovum into two blastomeres, and continuing in the larger animals to the formation of an innumerable multitude of cellular units. In the second place there is present in the ovum a form-building power of such a character that the great complex of cells arising from it produces not a heterogeneous mass, but a definite organism of the same structure, organ for organ and tissue for tissue, as the parent form. The ovum of a starfish develops into a starfish, the ovum of a dog into a dog, and the ovum of man into a human being. Herein lies the great problem of heredity. The mere multiplication of cells by direct or indirect division is not beyond the range of a conceivable mechanical explanation. Given the properties of assimilation and contractility it is possible that the act of cell-division may be traced to purely physical and chemical causes, and already cytological work is opening the way to credible hypotheses of this character. But the phenomena of heredity, on the other hand, are too complex and mysterious to justify any immediate expectation that they can be explained in terms of the known properties of matter. The crude theories of earlier times have not stood the test of investigation by modern methods, the microscopic anatomy of both ovum and sperm showing that they are to all appearances simple cells that exhibit no visible signs of the wonderful potentialities contained within them. Histological and experimental investigation has, however, cleared away some of the difficulties formerly surrounding the subject, for it has shown with a high degree of probability that the power of hereditary transmission resides in a particular substance in the nucleus, namely in the so-called chromatin material that forms the chromosomes. The fascinating observations<sup>1</sup> that have led to this conclusion promise to open up a new field of experimentation and speculation. It seems to be possible to study heredity by accepted scientific methods, and we may therefore hope that in time more light will be thrown upon the conditions of its existence and possibly upon the nature of the forces concerned in its production.

In the facts of consciousness, lastly, we are confronted with a problem seemingly more difficult than heredity. In ourselves we recognize different states of consciousness following upon the physiological activity of certain parts of the central nervous system. We know, or think we know, that these so-called psychical states are correlated with changes in the protoplasmic material of the cortical cells of the cerebral hemispheres. When these cells

<sup>1</sup> Wilson: *The Cell in Development and Inheritance*, 1896.

are stimulated, psychical states result; when they are injured or removed, psychical activity is depressed or destroyed altogether according to the extent of the injury. From the physiological standpoint it would seem to be as justifiable to assert that consciousness is a property of the cortical nerve-cells as it is to define contractility as a property of muscle-tissue. But the shortening of a muscle is a physical phenomenon that can be observed with the senses—be measured and theoretically explained in terms of the known properties of matter. Psychical states are, however, removed from such methods of study; they are subjective, and cannot be measured or weighed or otherwise estimated with sufficient accuracy and completeness in terms of our units of energy or matter. There must be a causative connection between the objective changes in the brain-cells and the corresponding states of consciousness, but the nature of this connection remains hidden from us; and so hopeless does the problem seem that some of our profoundest thinkers have not hesitated to assert that it can never be solved. Whether or not consciousness is possessed by all animals it is impossible to say. In ourselves we know that it exists, and we have convincing evidence, from their actions, that it is possessed by many of the higher animals. But as we descend in the scale of animal forms the evidence becomes less impressive. It is true that even the simplest forms of animal life exhibit reactions of an apparently purposeful character which some have explained upon the simple assumption that these animals are endowed with consciousness or a psychical power of some sort. All such reactions, however, may be explained, as in the case of reflex actions from the spinal cord, upon purely mechanical principles, as the necessary response of a definite physical or chemical mechanism to a definite stimulus. To assume that in all cases of this kind conscious processes are involved amounts to making psychical activity one of the universal and primitive properties of protoplasm whether animal or vegetable, and indeed by the same kind of reasoning there would seem to be no logical objection to extending the property to all matter whether living or dead. All such views are of course purely speculative. As a matter of fact we have no means of proving or disproving, in a scientific sense, the existence of consciousness in lower forms of life. To quote an appropriate remark of Huxley's made in discussing this same point with reference to the crayfish, "Nothing short of being a crayfish would give us positive assurance that such an animal possesses consciousness." The study of psychical states in ourselves, for reasons which have been suggested above, does not usually form a part of the science of physiology. The matter has been referred to here simply because consciousness is a fact that our science cannot as yet explain.

So far, some of the broad principles of physiology have been considered—principles which are applicable with more or less modification to all forms of animal life and which make the basis of what is known as general physiology. It must be borne in mind, however, that each particular organism possesses a special physiology of its own, which consists in part in a study of the properties exhibited by the particular kinds or variations of protoplasm in each individual, and in large part also in a study of the various mechan-



isms existing in each animal. In the higher animals, particularly, the combinations of various tissues and organs into complex mechanisms such as those of respiration, circulation, digestion, or vision, differ more or less in each group and to a minor extent in each individual of any one species. It follows, therefore, that each animal has a special physiology of its own, and in this sense we may speak of a special human physiology. It need scarcely be said that the special physiology of man is very imperfectly known. Books like the present one, which profess to treat of human physiology, contain in reality a large amount of general and special physiology that has been derived from the study of lower animal forms upon which exact experimentation is possible. Most of our fundamental knowledge of the physiology of the heart and of muscles and nerves has been derived from experiments upon frogs and similar animals, and much of our information concerning the mechanisms of circulation, digestion, etc. has been obtained from a study of other mammalian forms. We transfer this knowledge to the human being, and in general without serious error, since the connection between man and related mammalia is as close on the physiological as it is on the morphological side, and the fundamental or general physiology of the tissues seems to be everywhere the same. Gradually, however, the material for a genuine special human physiology is being acquired. In many directions special investigation upon man is possible; for instance, in the study of the localization of function in the cerebral cortex, or the details of body metabolism as obtained by examination of the excreta, or the peculiarities of vaso-motor regulation as revealed by the use of plethysmographic methods, or the physiological optics of the human eye. This special information, as rapidly as it is obtained, is incorporated into the text-books of human physiology, but the fact remains that the greater part of our so-called human physiology is founded upon experiments upon the lower animals.

Physiology as a science is confessedly very imperfect; it cannot compare in exactness with the sciences of physics and chemistry. This condition of affairs need excite no surprise when we remember the very wide field that physiology attempts to cover, a field co-ordinate in extent with the physics as well as the chemistry of dead matter, and the enormous complexity and instability of the form of matter that it seeks to investigate. The progress of physiology is therefore comparatively slow. The present era seems to be one mainly of accumulation of reliable data derived from laborious experiments and observations. The synthesis of these facts into great laws or generalizations is a task for the future. Corresponding with the diversity of the problems to be solved we find that the methods employed in physiological research are manifold in character. Inasmuch as animal organisms are composed either of single cells or aggregates of cells, it follows that every anatomical detail with regard to the organization of the cell itself or the connection between different cells, and every advance in our knowledge of the arrangement of the tissues and organs that form the more complicated mechanisms, is of immediate value to physiology. The microscopic anatomy of the cell (a branch of

histology that is frequently designated by the specific name of cytology), general histology, and gross anatomical dissection are therefore frequently employed in physiological investigations, and form what may be called the observational side of the science. On the other hand, we have the experimental methods, that seek to discover the properties and functional relationships of the tissues and organs by the use of direct experiments. These experiments may be of a surgical character, involving the extirpation or destruction or alteration of known parts by operations upon the living animal, or they may consist in the application of the accepted methods of physics and chemistry to the living organism. The physical methods include the study of the physical properties of living matter and the interpretation of its activity in terms of known physical laws, and also the use of various kinds of physical apparatus such as manometers, galvanometers, etc. for recording with accuracy the phenomena exhibited by living tissues. The chemical methods imply the application of the synthetic and analytic operations of chemistry to the study of the composition and structure of living matter and the products of its activity. The study of the subjective phenomena of conscious life—in fact, the whole question of the psychic aspects or properties of living matter—for reasons that have been mentioned is not usually included in the science of physiology, although strictly speaking it forms an integral part of the subject. This province of physiology has, however, been organized into a separate science, psychology, although the boundary line between psychology as it exists at present and the scientific physiology of the nervous system cannot always be sharply drawn.

It follows clearly enough from what has been said of the methods used in animal physiology that even an elementary acquaintance with the subject as a science requires some knowledge of general histology and anatomy, human as well as comparative, of physics, and of chemistry. When this preliminary training is lacking, physiology cannot be taught as a science; it becomes simply a heterogeneous mass of facts, and fails to accomplish its function as a preparation for the scientific study of medicine. The mere facts of physiology are valuable, indeed indispensable, as a basis for the study of the succeeding branches of the medical curriculum, but in addition the subject, properly taught, should impart a scientific discipline and an acquaintance with the possible methods of experimental medicine; for among the so-called experimental branches of medicine physiology is the most developed and the most exact, and serves as a type, so far as methods are concerned, to which the others must conform.





## II. BLOOD AND LYMPH.

### BLOOD.

#### A. GENERAL PROPERTIES: PHYSIOLOGY OF THE CORPUSCLES.

THE blood of the body is contained in a practically closed system of tubes, the *blood-vessels*, within which it is kept circulating by the force of the heart-beat. The blood is usually spoken of as the nutritive liquid of the body, but its functions may be stated more explicitly, although still in quite general terms, by saying that it carries to the tissues food-stuffs after they have been properly prepared by the digestive organs; that it transports to the tissues oxygen absorbed from the air in the lungs; that it carries off from the tissues various waste products formed in the processes of disassimilation; that it is the medium for the transmission of the internal secretion of certain glands; and that it aids in equalizing the temperature and water contents of the body. It is quite obvious, from these statements, that a complete consideration of the physiological relations of the blood would involve substantially a treatment of the whole subject of physiology. It is proposed, therefore, in this section to treat the blood in a restricted way—to consider it, in fact, as a tissue in itself, and to study its composition and properties without special reference to its nutritive relationship to other parts of the body.

**Histological Structure.**—The blood is composed of a liquid part, the *plasma*, in which float a vast number of microscopic bodies, the *blood-corpuscles*. There are at least three different kinds of corpuscles, known respectively as the *red corpuscles*; the *white corpuscles* or *leucocytes*, of which in turn there are a number of different kinds; and the *blood-plates*. As the details of structure, size, and number of these corpuscles belong properly to textbooks on histology, they will be mentioned only incidentally in this section when treating of the physiological properties of the corpuscles. Blood-plasma, when obtained free from corpuscles, is perfectly colorless in thin layers—for example, in microscopic preparations; when seen in large quantities it shows a slightly yellowish tint, the depth of color varying with different animals. This color is due to the presence in small quantities of a special pigment, the nature of which is not definitely known. The red color of blood is not due, therefore, to coloration of the blood-plasma, but is caused by the mass of red corpuscles held in suspension in this liquid. The proportion by bulk of plasma to corpuscles is usually given, roughly, as two to one.

**Blood-serum and Defibrinated Blood.**—In connection with the explanation of the term “blood-plasma” just given, it will be convenient to define briefly the terms “blood-serum” and “defibrinated blood.” Blood, after it escapes from the vessels, usually clots or coagulates; the nature of this process is



discussed in detail on p. 54. The clot, as it forms, gradually shrinks and squeezes out a clear liquid to which the name *blood-serum* is given. Serum resembles the plasma of normal blood in general appearance, but differs from it in composition, as will be explained later. At present we may say, by way of a preliminary definition, that blood-serum is the liquid part of blood after coagulation has taken place, as blood-plasma is the liquid part of blood before coagulation has taken place. If shed blood is whipped vigorously with a rod or some similar object while it is clotting, the essential part of the clot—namely, the fibrin—forms differently from what it does when the blood is allowed to coagulate quietly; it is deposited in shreds on the whipper. Blood that has been treated in this way is known as *defibrinated blood*. It consists of blood-serum plus the red and white corpuscles, and as far as appearances go it resembles exactly normal blood; it has lost, however, the power of clotting. A more complete definition of these terms will be given after the subject of coagulation has been treated.

**Reaction.**—The reaction of blood is alkaline, owing mainly to the alkaline salts, especially the carbonates of soda, dissolved in the plasma. The degree of alkalinity varies with different animals: reckoned as  $\text{Na}_2\text{CO}_3$ , the alkalinity of dog's blood corresponds to 0.2 per cent. of this salt; of human blood, 0.35 per cent. The alkaline reaction of blood is very easily demonstrated upon clear plasma free from corpuscles, but with normal blood the red color prevents the direct application of the litmus test. A number of simple devices have been suggested to overcome this difficulty. For example, the method employed by Zuntz is to soak a strip of litmus-paper in a concentrated solution of  $\text{NaCl}$ , to place on this paper a drop of blood, and, after a few seconds, to remove the drop with a stream of water or with a piece of filter-paper. The alkaline reaction becomes rapidly less marked after the blood has been shed; it varies also slightly under different conditions of normal life and in certain pathological conditions. After meals, for instance, during the act of digestion, it is said to be increased, while, on the contrary, exercise causes a diminution. In no case, however, does the reaction become acid. For details of the methods used for quantitative determinations of the alkalinity of human blood, reference must be made to original sources.<sup>1</sup>

**Specific Gravity.**—The specific gravity of human blood in the adult male may vary from 1041 to 1067, the average being about 1055. Jones<sup>2</sup> made a careful study of the variations in specific gravity of human blood under different conditions of health and disease, making use of a simple method which requires only a few drops of blood for each determination. He found that the specific gravity varies with age and sex, that it is diminished after eating and is increased by exercise, that it falls slowly during the day and rises gradually during the night, and that it varies greatly in individuals, "so much so that a specific gravity which is normal for one may be a sign of disease in another." The specific gravity of the corpuscles is slightly greater

<sup>1</sup> Wright: *The Lancet*, 1897, p. 8; Winternitz: *Zeitschrift für physiol. Chemie*, 1891, Bd. 15, S. 505.

<sup>2</sup> *Journal of Physiology*, 1891, vol. xii., p. 299.

than that of the plasma. For this reason the corpuscles in shed blood, when its coagulation is prevented or retarded, tend to settle to the bottom of the containing utensil, leaving a more or less clear layer of supernatant plasma. Among themselves, also, the corpuscles differ slightly in specific gravity, the red corpuscles being heaviest and the blood-plates being lightest.

**Red Corpuscles.**—The red corpuscles in man and in all the mammalia, with the exception of the camel and other members of the group Camelidae, are biconcave circular disks without nuclei; in the Camelidae they have an elliptical form. Their average diameter in man is given as  $7.7\mu$  ( $1\mu = 0.001$  of a mm.); their number, which is usually reckoned as so many in a cubic millimeter, varies greatly under different conditions of health and disease. The average number is given as 5,000,000 per cubic mm. for males and 4,500,000 for females. The red color of the corpuscles is due to the presence in them of a pigment known as "hæmoglobin." Owing to the minute size of the corpuscles, their color when seen singly under the microscope is a faint yellowish-red, but when seen in mass they exhibit the well-known blood-red color, which varies from scarlet in arterial blood to purplish-red in venous blood, this variation in color being dependent upon the amount of oxygen contained in the blood in combination with the hæmoglobin. Speaking generally, the function of the red corpuscles is to carry oxygen from the lungs to the tissues. This function is entirely dependent upon the presence of hæmoglobin, which has the power of combining easily with oxygen gas. The physiology of the red corpuscles, therefore, is largely contained in a description of the properties of hæmoglobin.

**Condition of the Hæmoglobin in the Corpuscle.**—The finer structure of the red corpuscle is not completely known. It is commonly believed that the corpuscle consists of two substances—a delicate, extensible, colorless protoplasmic material, which gives to the corpuscle its shape and which is known as the *stroma*, and the hæmoglobin. The latter constitutes the bulk of the corpuscle, forming as much as 95 per cent. of the solid matter. It was formerly thought that hæmoglobin is disseminated as such in the interstices of the porous spongy stroma, but there seem to be reasons now for believing that it is present in the corpuscles in some combination the nature of which is not fully known. This belief is based upon the fact that Hoppe-Seyler<sup>1</sup> has shown that hæmoglobin while in the corpuscles exhibits certain minor differences in properties as compared with hæmoglobin outside the corpuscles. In various ways the compound of hæmoglobin in the corpuscles may be destroyed, the hæmoglobin being set free and passing into solution in the plasma. Blood in which this change has occurred is altered in color and is known as "laky blood." In thin layers it is transparent, whereas normal blood with the hæmoglobin still in the corpuscles is quite opaque even in very thin strata. Blood may be made laky by the addition of ether, of chloroform, of bile or the bile acids, of the serum of other animals, by an excess of water, by alternately freezing and thawing, and by a number of other methods. In connection with two of these methods of discharging hæmoglobin from the

<sup>1</sup> *Zeitschrift für physiologische Chemie*, Bd. xiii, 1889, S. 477.



corpuscles there have come into use in current medical and physiological literature two technical terms which it may be well to attempt to define.

*Globulicidal Action of Serum.*—It was shown first by Landois that the serum of one animal may have the property of destroying the red corpuscles in the blood of another animal, thus making the blood laky. This fact, which has since been investigated more fully, is now designated under the term of "globulicidal" action of the serum. It has been found that different kinds of serum show different degrees of globulicidal activity, and that white as well as red corpuscles may be destroyed. Dog's serum or human serum is strongly globulicidal to rabbit's blood. It would seem that this action is not due to mere variations in the amounts of inorganic salts in the different kinds of serum, since the remarkable fact has been discovered that heating serum to 55° or 60° C. for a few minutes destroys its globulicidal action, although such treatment causes no coagulation of the proteids nor any visible change in the liquid. Moreover, it is known that foreign serum injected into the veins of a living animal may exert a marked toxic effect that cannot be explained solely by its globulicidal action—for instance, 7 to 14 c.c. of fresh dog's serum will suffice to kill a rabbit—and lastly, serum is known to exert a similar destructive effect on bacteria, its so-called bactericidal action. These three effects of serum, globulicidal, bactericidal and toxic, seem all to be destroyed by heating to 50°–60° C., and it is possible that they are all traceable to the existence in the blood of some proteid substance, an alexine, which is present in small quantity and is different for each species of animal, the material in the blood of one species being more or less globulicidal and toxic, as a rule, to the tissues of another species.<sup>1</sup>

*Isotonic Solutions.*—When blood or defibrinated blood is diluted with water, a point is soon reached at which hæmoglobin begins to pass out of the corpuscles into the plasma or the serum, and the blood begins to appear laky. It appears that the liquid surrounding the corpuscles must have a certain concentration as regards salts or other soluble substances, such as sugar, in order to prevent the entrance of water into the substance of the corpuscle. Normally the substance of the red corpuscle possesses a certain osmotic pressure which may be supposed to be equal to that of the plasma by which it is surrounded, so that the interchange of water between them is at an equilibrium. If the concentration of the outside liquid is diminished, this equilibrium is destroyed and water passes into the corpuscle; if the dilution has been sufficient, enough water passes into the corpuscle to make it swell and eventually to force out the hæmoglobin. Liquids containing inorganic salts, or other soluble substances that possess an osmotic pressure sufficient to prevent the imbibition of water by the corpuscles, are said to be "isotonic to the corpuscles." Red corpuscles suspended in such liquids do not change in shape nor lose their hæmoglobin. When solutions of different substances are compared from this standpoint, it is found that the concentration necessary varies with the substance used. Thus, a solution of NaCl of 0.64 per cent. is isotonic

<sup>1</sup> For a recent paper and the literature see Friedenthal and Lewandowsky, *Archiv für Physiologie*, 1899, S. 531.

with a solution of sugar of 5.5 per cent. or a solution of  $\text{KNO}_3$  of 1.09 per cent. When placed in any of these three solutions red corpuscles do not take up water—at least not in quantities sufficient to discharge the hæmoglobin. For a more complete account of these relations the reader is referred to original sources (Hamburger<sup>1</sup>). A solution whose osmotic pressure is lower than that of blood-plasma is said to be hypo-isotonic or hypotonic to blood. Such solutions may cause the blood to lake. Solutions of a higher osmotic pressure than that of the plasma are spoken of as hyper-isotonic or hypertonic. Whenever it is necessary to dilute shed blood or to inject any quantity of a neutral liquid into the circulation care must be taken to have the solution isotonic with the blood. (See p. 65 for an explanation of the term osmotic pressure.)

**Nature and Amount of Hæmoglobin.**—Hæmoglobin is a very complex substance belonging to the group of combined proteids. (For the definition and classification of proteids, as well as for the purely chemical properties of hæmoglobin and its derivatives, reference must be made to the section on "The Chemistry of the Body.") When decomposed in various ways hæmoglobin breaks up into a proteid (globin, 86 to 96 per cent.), a simpler pigment (hæmatin, 4 per cent.), and an unknown residue.<sup>2</sup> When the decomposition takes place in the absence of oxygen, the products formed are globin and hæmochromogen, instead of globin and hæmatin. Hæmochromogen in the presence of oxygen quickly undergoes oxidation to the more stable hæmatin. Hoppe-Seyler has shown that hæmochromogen possesses the chemical grouping which gives to hæmoglobin its power of combining readily with oxygen and its distinctive absorption spectrum. On the basis of facts such as these, hæmoglobin may be defined as a compound of a proteid body with hæmochromogen. It seems, then, that although the hæmochromogen portion is the essential thing, giving to the molecule of hæmoglobin its valuable physiological properties as a respiratory pigment, yet in the blood-corpuscles this substance is incorporated into the much larger and more unstable molecule of hæmoglobin, whose behavior toward oxygen is different from that of the hæmochromogen itself, the difference being mainly in the fact that the hæmoglobin as it exists in the corpuscles forms with oxygen a comparatively feeble combination that may be broken up readily with liberation of the gas.

Hæmoglobin is widely distributed throughout the animal kingdom, being found in the blood-corpuscles of mammalia, birds, reptiles, amphibia, and fishes, and in the blood or blood-corpuscles of many of the invertebrates. The composition of its molecule is found to vary somewhat in different animals, so that, strictly speaking, there are probably a number of different forms of hæmoglobin—all, however, closely related in chemical and physiological properties. Elementary analysis of dog's hæmoglobin shows the following percentage composition (Jaquet): C 53.91, H 6.62, N 15.98, S 0.542, Fe 0.333, O 22.62. Its molecular formula is given as  $\text{C}_{750}\text{H}_{1205}\text{N}_{195}\text{S}_3\text{FeO}_{210}$ , which would make the molecular weight 16,669. Other estimates are given of

<sup>1</sup> Du Bois-Reymond's *Archiv für Physiologie*, 1886, S. 476; 1887, S. 31.

<sup>2</sup> See Schulz, *Zeitschrift für physiol. Chemie*, Bd. 24; also Lauraw, *ibid.*, Bd. 26.



the molecular formula, but they agree at least in showing that the molecule is of enormous size. The molecular formula for hæmochromogen is much simpler; one estimate makes it  $C_{34}H_{36}N_4FeO_5$ . The exact amount of hæmoglobin in human blood varies naturally with the individual and with different conditions of life. According to Preyer,<sup>1</sup> the average amount for the adult male is 14 grams of hæmoglobin to each 100 grams of blood. It is estimated that in the blood of a man weighing 68 kilos. there are contained about 750 grams of hæmoglobin, which is distributed among some twenty-five trillions of corpuscles, giving a total superficial area of about 3200 square meters. Practically all of this large surface of hæmoglobin is available for the absorption of oxygen from the air in the lungs, for, owing to the great number and the minute size of the capillaries, the blood, in passing through a capillary area, becomes subdivided to such an extent that the red corpuscles stream through the capillaries, one may say, in single file. In circulating through the lungs, therefore, each corpuscle becomes exposed more or less completely to the action of the air, and the utilization of the entire quantity of hæmoglobin must be nearly perfect. It may be worth while to call attention to the fact that the biconcave form of the red corpuscle increases the superficies of the corpuscle and tends to make the surface exposure of the hæmoglobin more complete.

**Compounds with Oxygen and other Gases.**—Hæmoglobin has the property of uniting with oxygen gas in certain definite proportions, forming a true chemical compound. This compound is known as *oxyhæmoglobin*; it is formed whenever blood or hæmoglobin solutions are exposed to air or otherwise brought into contact with oxygen. Each molecule of hæmoglobin is supposed to combine with one molecule of oxygen, and it is usually estimated that 1 gram of dried hæmoglobin (dog) can take up 1.59 c.c. of oxygen measured at 0° C. and 760 mm. of barometric pressure, although according to a later determination by Hüfner,<sup>2</sup> the O-capacity of the Hb of ox's blood is only 1.34 c.c. O to each gram of Hb. Oxyhæmoglobin is not a very firm compound. If placed in an atmosphere containing no oxygen, it will be dissociated, giving off free oxygen and leaving behind hæmoglobin, or, as it is often called by way of distinction, "*reduced hæmoglobin*." This power of combining with oxygen to form a loose chemical compound, which in turn can be dissociated easily when the oxygen-pressure is lowered, makes possible the function of hæmoglobin in the blood as the carrier of oxygen from the lungs to the tissues. The details of this process are described in the section on Respiration. Hæmoglobin forms with carbon-monoxide gas (CO) a compound, similar to oxyhæmoglobin, which is known as *carbon-monoxide hæmoglobin*. In this compound also the union takes place in the proportion of one molecule of hæmoglobin to one molecule of the gas. The compound formed differs, however, from oxyhæmoglobin in being much more stable, and it is for this reason that the breathing of carbon monoxide gas is liable to prove fatal. The CO unites with the hæmoglobin, forming a firm compound; the tissues of the body are

<sup>1</sup> *Die Blutkrystalle*, Jena, 1871.

<sup>2</sup> *Archiv für Physiologie*, 1894, S. 130.

thereby prevented from obtaining their necessary oxygen, and death results from suffocation or asphyxia. Carbon monoxide forms one of the constituents of coal-gas. The well-known fatal effect of breathing coal-gas for some time, as in the case of individuals sleeping in a room where gas is escaping, is traceable directly to the carbon monoxide. Nitric oxide (NO) forms also with hæmoglobin a definite compound that is even more stable than the CO-hæmoglobin; if, therefore, this gas were brought into contact with the blood, it would cause death in the same way as the CO.

Oxyhæmoglobin, carbon-monoxide hæmoglobin, and nitric-oxide hæmoglobin are similar compounds. Each is formed, apparently, by a definite combination of the gas with the hæmochromogen portion of the hæmoglobin molecule, and a given weight of hæmoglobin unites presumably with an equal volume of each gas. In marked contrast to these facts, Bohr<sup>1</sup> has shown that hæmoglobin forms a compound with carbon-dioxide gas, *carbo-hæmoglobin*, in which the quantitative relationship of the gas to the hæmoglobin differs from that shown by oxygen. In a mixture of O and CO<sub>2</sub> each gas is absorbed by hæmoglobin solutions independently of the other, so that a solution of hæmoglobin nearly saturated with oxygen can unite with as much CO<sub>2</sub> as though it held no oxygen in combination. Bohr suggests, therefore, that the O and the CO<sub>2</sub> must unite with different portions of the hæmoglobin—the oxygen with the pigment portion, the hæmochromogen, and the CO<sub>2</sub> possibly with the proteid portion. It seems probable that hæmoglobin plays a part in the transportation of the carbon dioxide as well as the oxygen of the blood, but its exact value in this respect as compared with the blood-plasma, which also acts as a carrier of CO<sub>2</sub>, has not been definitely determined (see Respiration).

**Presence of Iron in the Molecule.**—It is probable that iron is quite generally present in the animal tissues in connection with nuclein compounds, but its existence in hæmoglobin is noteworthy because it has long been known and because the important property of combining with oxygen seems to be connected with the presence of this element. According to the analyses made, the proportion of iron in hæmoglobin varies somewhat in different animals: the figures given are from 0.335 to 0.47 per cent. The amount of hæmoglobin in blood may be determined, therefore, by making a quantitative determination of the iron. The amount of oxygen with which hæmoglobin will combine may be expressed by saying that one molecule of oxygen will be fixed for each atom of iron in the hæmoglobin molecule. In the decomposition of hæmoglobin into globulin and hæmatin, which has been spoken of above, the iron is retained in the hæmatin.

**Crystals.**—Hæmoglobin may be obtained readily in the form of crystals (Fig. 1). As usually prepared, these crystals are really oxyhæmoglobin, but it has been shown that reduced hæmoglobin also crystallizes, although with more difficulty. Hæmoglobin from the blood of different animals varies to a marked degree in respect to the power of crystallization. From the blood of the rat, dog, cat, guinea-pig, and horse, crystals are readily obtained, while hæmoglobin from the blood of man and of most of the vertebrates crystallizes

<sup>1</sup> *Skandinavisches Archiv für Physiologie*, 1892, Bd. 3, S. 47.



much less easily. Methods for preparing and purifying these crystals will be found in works on Physiological Chemistry. To obtain specimens quickly for examination under the microscope, one of the most certain methods is to take some blood from one of the animals whose hæmoglobin crystallizes

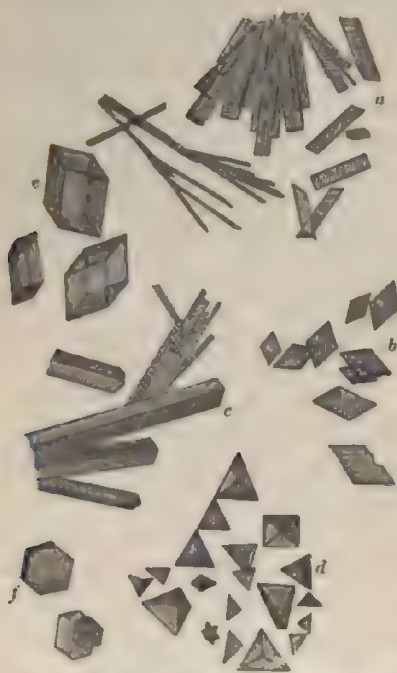


FIG. 1.—Crystallized hæmoglobin (after Frey): *a, b*, crystals from venous blood of man; *c*, from the blood of a cat; *d*, from the blood of a guinea-pig; *e*, from the blood of a hamster; *f*, from the blood of a squirrel.

easily, place it in a test-tube, add to it a few drops of ether, shake the tube thoroughly until the blood becomes laky—that is, until the hæmoglobin is discharged into the plasma—and then place the tube on ice until the crystals are deposited. Small portions of the crystalline sediment may then be removed to a glass slide for examination. Hæmoglobin from different animals varies not only as to the ease with which it crystallizes, but in some cases also as to the form that the crystals take. In man and in most of the mammalia hæmoglobin is deposited in the form of rhombic prisms; in the guinea-pig it crystallizes in tetrahedra (*d*, Fig. 1), and in the squirrel in hexagonal plates. The crystals are readily soluble in water, and by repeated crystallizations the hæmoglobin may be obtained perfectly pure.

As in the case of other soluble proteid-like bodies, solutions of hæmoglobin are precipitated by alcohol, by mineral acids, by salts of the heavy metals, by boiling,

etc. Notwithstanding the fact that hæmoglobin crystallizes so readily, it is not easily dialyzable, behaving in this respect like proteids and other colloidal bodies. The compounds which hæmoglobin forms with carbon monoxide (CO) and nitric oxide (NO) are also crystallizable, the crystals being isomorphous with those of oxyhæmoglobin.

**Absorption Spectra.**—Solutions of hæmoglobin and its derivative compounds, when examined with a spectroscope, give distinctive absorption bands. A brief account of the principle and arrangement of the spectroscope, although unnecessary for those familiar with the elements of Physics, is given by way of introduction to the description of these absorption bands.

Light, when made to pass through a glass prism, is broken up into its constituent rays, giving the play of rainbow colors known as the *spectrum*. A spectroscope is an apparatus for producing and observing a spectrum. A simple form, which illustrates sufficiently well the construction of the apparatus, is shown in Figure 2, *r* being the glass prism giving the spectrum. Light falls upon this prism through the tube (*A*) to the left, known as the "collimator tube." A slit at the end of this tube (*B*) admits a narrow slice of light—lamplight or sunlight—which then, by means of a convex lens at the other end of the tube, is made to fall upon the prism

(P) with its rays parallel. In passing through the prism the rays are dispersed by unequal refraction, giving a spectrum. The spectrum thus produced is examined by the observer with the aid of the telescope (B). When the telescope is properly focussed for the rays entering it from the prism (P), a clear picture of the spectrum is seen. The length of the spectrum will depend upon the nature and the number of prisms through which the light is made to pass. For ordinary purposes a short spectrum is preferable for hæmoglobin bands, and a spectroscope with one prism is generally used. If the source of light is a lamp-flame of some kind, the spectrum is continuous, the colors gradually merging one into another from red to violet. If sunlight is used, the spectrum will be crossed by a number of narrow dark lines known as the "Fraunhofer lines"

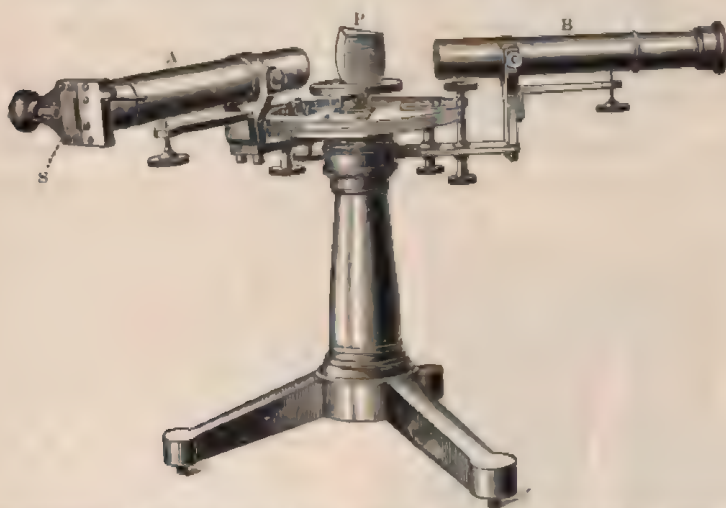


FIG. 2.—Spectroscope: P, the glass prism; A, the collimator tube, showing the slit (s) through which the light is admitted; B, the telescope for observing the spectrum.

(see Pl. I., *Frontispiece*, for an illustration in colors of the solar spectrum). The position of these lines in the solar spectrum is fixed, and the more distinct ones are designated by letters of the alphabet, A, B, C, D, E, etc., as shown in the charts below. If while using solar light or an artificial light a solution of any substance which gives absorption bands is so placed in front of the slit that the light is obliged to traverse it, the spectrum as observed through the telescope will show one or more narrow or broad black bands, that are characteristic of the substance used and constitute its absorption spectrum. The positions of these bands may be designated by describing their relations to the Fraunhofer lines, or more directly by stating the wave-lengths of the portions of the spectrum between which absorption takes place. Some spectroscopes are provided with a scale of wave-lengths superposed on the spectrum, and when properly adjusted this scale enables one to read off directly the wave-lengths of any part of the spectrum.

When very dilute solutions of oxyhæmoglobin are examined with the spectroscope, two absorption bands appear, both occurring in the portion of the spectrum included between the Fraunhofer lines D and E. The band nearer the red end of the spectrum is known as the " $\alpha$ -band;" it is narrower, darker, and more clearly defined than the other, the " $\beta$ -band" (Fig. 3, and also Pl. I. spectrum 4). With a solution containing 0.09 per cent. of oxyhæmoglobin, and examined in layers one centimeter thick, the  $\alpha$ -band extends over the part of the spectrum included between the wave-lengths  $\lambda$  583



(583 millionths of a millimeter) and  $\lambda$  571, and the  $\beta$ -band between  $\lambda$  550 and  $\lambda$  532 (Gamble). The width and distinctness of the bands vary naturally with the concentration of the solution used (see Pl. I. spectra 2, 3, 4, and 5),

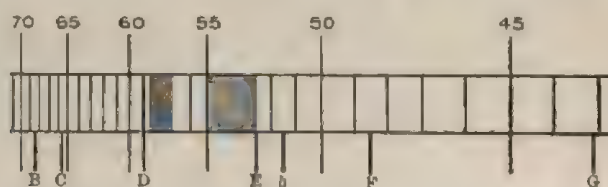


FIG. 3.—Diagrammatic representation of the absorption spectrum of oxyhemoglobin (after Rollett). The numerals give the wave-lengths in hundred-thousandths of a millimeter; the letters show the positions of the more prominent Fraunhofer lines of the solar spectrum. The red end of the spectrum is to the left. The  $\alpha$ -band is to the right of D, the  $\beta$ -band to the left of E.

or, if the concentration remains the same, with the width of the stratum of liquid through which the light passes. With a certain minimal percentage of

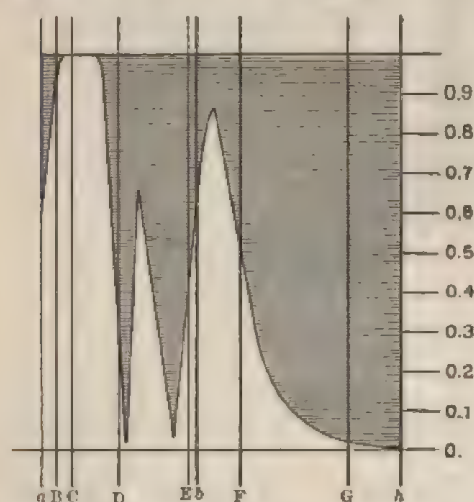


FIG. 4.—Diagram to show the variations in the absorption spectrum of oxyhemoglobin with varying concentrations of the solution (after Rollett). The numbers to the right give the strength of the oxyhemoglobin solution in percentages; the letters give the positions of the Fraunhofer lines. To ascertain the amount of absorption for any given concentration up to 1 per cent., draw a horizontal line across the diagram at the level corresponding to the concentration. Where this line passes through the shaded part of the diagram absorption takes place, and the width of the absorption bands is seen at once. The diagram shows clearly that the amount of absorption increases as the solutions become more concentrated, especially the absorption of the blue end of the spectrum. It will be noticed that with concentrations between 0.6 and 0.7 per cent. the two bands between D and E fuse into one.

between the lines D and E; its relations to these lines and the bands of oxyhemoglobin are shown in Figure 5 and in Pl. I. spectrum 6. The

oxyhemoglobin (less than 0.01 per cent.) the  $\beta$ -band is lost and the  $\alpha$ -band is very faint in layers one centimeter thick. With stronger solutions the bands become darker and wider and finally fuse, while some of the extreme red end and a great deal of the violet end of the spectrum is also absorbed. The variations in the absorption spectrum with differences in concentration are clearly shown in the accompanying illustration from Rollett<sup>1</sup> (Fig. 4); the thickness of the layer of liquid is supposed to be one centimeter. The numbers on the right indicate the percentage strength of the oxyhemoglobin solutions. It will be noticed that the absorption which takes place as the concentration of the solution increases affects the red-orange end of the spectrum last of all.

Solutions of reduced hemoglobin examined with the spectroscope show only one absorption band, known sometimes as the " $\gamma$ -band." This band lies also in the portion of the spectrum included

<sup>1</sup> Hermann's *Handbuch der Physiologie*, Bd. iv., 1880.

$\gamma$ -band is much more diffuse than the oxyhæmoglobin bands, and its limits therefore, especially in weak solutions, are not well defined; in solutions of blood diluted 100 times with water, which would give a hæmoglobin solution of about 0.14 per cent., the absorption band lies in the part of the spectrum included between the wave-lengths  $\lambda$  572 and  $\lambda$  542. The width

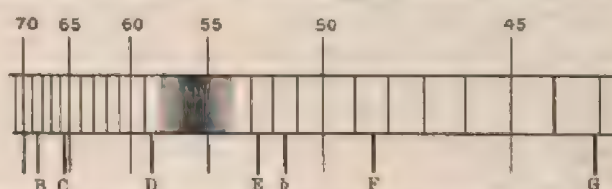


FIG. 5.—Diagrammatic representation of the absorption spectrum of hæmoglobin (reduced hæmoglobin) (after Rollett). The numerals give the wave-lengths in hundred-thousandths of a millimeter; the letters show the positions of the more prominent Fraunhofer lines of the solar spectrum. The red end of the spectrum is to the left. The single diffuse absorption band lies between D and E.

and distinctness of this band vary also with the concentration of the solution. This variation is sufficiently well shown in the accompanying illustration (Fig. 6), which is a companion figure to the one just given for oxyhæmoglobin (Fig. 4). It will be noticed that the last light to be absorbed in this case is partly in the red end and partly in the blue, thus explaining the purplish color of hæmoglobin solutions and of venous blood. Oxyhæmoglobin solutions can be converted to hæmoglobin solutions, with a corresponding change in the spectrum bands, by placing the former in a vacuum or, more conveniently, by adding reducing solutions. The solutions most commonly used for this purpose are ammonium sulphide and Stokes's reagent.<sup>1</sup> If a solution of reduced hæmoglobin is shaken with air, it quickly changes to oxyhæmoglobin and gives two bands instead of one when examined through the spectroscope. Any given solution may be changed in this way from oxyhæmoglobin to hæmoglobin, and the reverse, a great number of times, thus demonstrating the facility with which hæmoglobin takes up and surrenders oxygen.

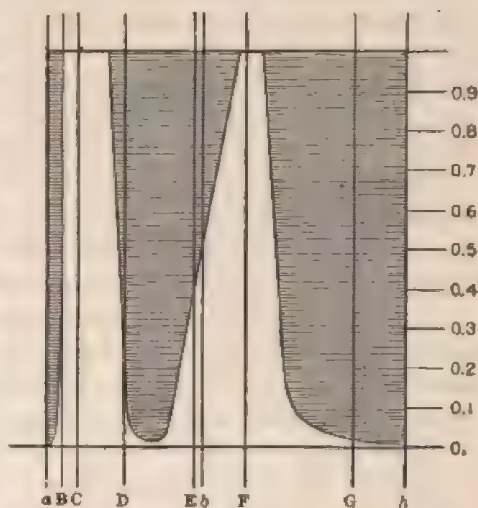


FIG. 6.—Diagram to show the variations in the absorption spectrum of reduced hæmoglobin with varying concentrations of the solution (after Rollett). The numbers to the right give the strength of the hæmoglobin solution in percentages; the letters give the positions of the Fraunhofer lines. For further directions as to the use of the diagram, see the description of Figure 4.

<sup>1</sup> Stokes's reagent is an ammoniacal solution of a ferrous salt. It is made by dissolving 2 parts (by weight) of ferrous sulphate, adding 3 parts of tartaric acid, and then ammonia to distinct alkaline reaction. A permanent precipitate should not be obtained.



Solutions of carbon-monoxide hæmoglobin also give a spectrum with two absorption bands closely resembling in position and appearance those of oxy-hæmoglobin (see Pl. I. spectrum 7). They are distinguished from the oxy-hæmoglobin bands by being slightly nearer the blue end of the spectrum, as may be demonstrated by observing the wave-lengths or, more conveniently, by superposing the two spectra. Moreover, solutions of carbon-monoxide hæmoglobin are not reduced to hæmoglobin by adding Stokes's liquid, two bands being still seen after such treatment. A solution of carbon-monoxide hæmoglobin suitable for spectroscopic examination may be prepared easily by passing ordinary coal-gas through a dilute oxyhæmoglobin solution for a few minutes and then filtering.

**Derivative Compounds of Hæmoglobin.**—A number of compounds directly related to hæmoglobin have been described, some of them being found normally in the body. Brief mention is made of the best known of these substances, but for the details of their preparation and chemical properties reference must be made to the section on "The Chemistry of the Body."

*Methæmoglobin* is a compound obtained by the action of oxidizing agents on hæmoglobin; it is frequently found, therefore, in blood stains or pathological liquids containing blood that have been exposed to the air for some time. It is now supposed to be identical in composition with oxyhæmoglobin, with the exception that the oxygen is held in more stable combination. Methæmoglobin crystallizes in the same form as oxyhæmoglobin, and has a characteristic spectrum (Pl. I. spectrum 8).

*Hæmochromogen* is the substance obtained when hæmoglobin is decomposed by acids or by alkalies in the absence of oxygen. It crystallizes and has a characteristic spectrum.

*Hæmatin* ( $C_{32}H_{30}N_4FeO_3$ ) is obtained when oxyhæmoglobin is decomposed by acids or by alkalies in the presence of oxygen. It is amorphous and has a characteristic spectrum (Pl. I. spectra 9 and 10).

*Hæmin* ( $C_{32}H_{30}N_4FeO_3HCl$ ) is a compound of hæmatin and HCl, and is readily obtained in crystalline form. It is much used in the detection of blood in medico-legal cases, as the crystals are very characteristic and are easily obtained from blood-clots or blood-stains, no matter how old these may be.

*Hæmatoporphyrin* ( $C_{16}H_{18}N_2O_3$ ) is a compound characterized by the absence of iron. It is frequently spoken of as "iron-free hæmatin." It is obtained by the action of strong sulphuric acid on hæmatin.

*Hæmatoidin* ( $C_{16}H_{18}N_2O_3$ ) is the name given to a crystalline substance found in old blood-clots, and formed undoubtedly from the hæmoglobin of the clotted blood. It has been shown to be identical with one of the bile-pigments, bilirubin. Its occurrence is interesting in that it demonstrates the relationship between hæmoglobin and the bile-pigments.

*Histohæmatins* are a group of pigments said to be present in many of the tissues—for example, the muscles. They are supposed to be respiratory pigments, and are related physiologically, and possibly chemically, to hæmoglobin. They have not been isolated, but their spectra have been described.

*Bile-pigments and Urinary Pigments*.—Hæmoglobin is regarded as the parent-substance of the bile-pigments and the urinary pigments.

**Origin and Fate of the Red Corpuscles.**—The mammalian red corpuscle is a cell that has lost its nucleus. It is not probable, therefore, that any given corpuscle lives for a great while in the circulation. This is made more certain by the fact that hæmoglobin is the mother-substance from which the bile-pigments are made, and, as these pigments are being excreted continually, it is fair to suppose that red corpuscles are as steadily undergoing disintegration in the blood-stream. Just how long the average life of the corpuscles is has not been determined, nor is it certain where and how they go to pieces. It has been suggested that their destruction takes place in the spleen, but the observations advanced in support of this hypothesis are not very numerous or conclusive. Among the reasons given for assuming that the spleen is especially concerned in the destruction of red corpuscles, the most weighty is the histological fact that one can sometimes find in teased preparations of spleen-tissue certain large cells which contain red corpuscles in their cell-substance in various stages of disintegration. It has been supposed that the large cells actually ingest the red corpuscles, selecting those, presumably, that are in a state of physiological decline. Against this idea a number of objections may be raised. Large leucocytes with red corpuscles in their interior are not found so frequently nor so constantly in the spleen as we would expect should be the case if the act of ingestion were constantly going on. There is some reason for believing, indeed, that the whole act of ingestion may be a post-mortem phenomenon; that is, after the cessation of the blood-stream the amœboid movements of the large leucocytes continue, while the red corpuscles lie at rest—conditions that are favorable to the act of ingestion. It may be added also that the blood of the splenic vein contains no hæmoglobin in solution, indicating that no considerable dissolution of red corpuscles is taking place in the spleen. Moreover, complete extirpation of the spleen does not seem to lessen materially the normal destruction of red corpuscles, if we may measure the extent of that normal destruction by the quantity of bile-pigment formed in the liver, remembering that hæmoglobin is the mother-substance from which the bile-pigments are derived. It is more probable that there is no special organ or tissue charged with the function of destroying red corpuscles, and that they undergo disintegration and dissolution while in the blood-stream and in any part of the circulation, the liberated hæmoglobin being carried to the liver and excreted in part as bile-pigment. The continual destruction of red corpuscles implies, of course, a continual formation of new ones. It has been shown satisfactorily that in the adult the organ for the reproduction of red corpuscles is the red marrow of bones. In this tissue *hæmatopoiesis*, as the process of formation of red corpuscles is termed, goes on continually, the process being much increased after hemorrhages and in certain pathological conditions. The details of the histological changes will be found in the text-books of histology. It is sufficient here to state simply that a group of nucleated colorless cells, erythroblasts, is found in the red marrow.



These cells multiply by karyokinesis, and the daughter-cells eventually produce hemoglobin in their cytoplasm, thus forming nucleated red corpuscles. The nuclei are subsequently lost, either by disintegration or, more likely, by extrusion, and the newly-formed non-nucleated red corpuscles are forced into the blood-stream, owing to a gradual change in their position during development caused by the growing hematopoietic tissue. When the process has been greatly accelerated, as after severe hemorrhages or in certain pathological conditions, red corpuscles still retaining their nuclei may be found in the circulating blood, having been forced out prematurely as it were. Such corpuscles may subsequently lose their nuclei while in the blood-stream. In the embryo, hematopoietic tissue is found in parts of the body other than the marrow, notably in the liver and spleen, which at that time serve as organs for the production of new red corpuscles. In the blood of the young embryo nucleated red corpuscles are at first abundant, but they become less numerous as the fetus grows older.<sup>1</sup>

**Variations in the Number of Red Corpuscles.**—The average number of red corpuscles for the adult male, as has been stated already, is usually given as 5,000,000 per cubic mm. The number is found to vary greatly, however. Outside of pathological conditions, in which the diminution in number may be extreme, differences have been observed in human beings under such conditions as the following: The number is less in females (4,500,000); it varies in individuals with the constitution, nutrition, and manner of life; it varies with age, being greatest in the fetus and in the newborn child; it varies with the time of the day, showing a distinct diminution after meals; in the female it varies somewhat in menstruation and in pregnancy, being slightly increased in the former and diminished in the latter condition. Perhaps the most interesting example of variation in the number of red corpuscles is that which occurs with changes in altitude. Residence in high altitudes is quickly followed by a marked increase in the number of red corpuscles. Viault<sup>2</sup> has shown that living in the mountains for two weeks at an altitude of 4392 meters caused an increase in the corpuscles from 5,000,000 to over 7,000,000 per cubic mm., and in the third week the number reached 8,000,000. The accuracy of this observation has been demonstrated since by many investigators. Some very careful work done under the direction of Miescher<sup>3</sup> has shown that a comparatively small increase in altitude, 700 meters, causes a marked increase in the number of red corpuscles and in the amount of hemoglobin, while return to a lower altitude quickly brings the blood back to its normal condition. From these observations it would seem that a diminished pressure of oxygen in the atmosphere stimulates the hematopoietic organs to greater activity, and it is interesting to compare this result with the effect of an actual loss of blood. In the latter case the production of red corpuscles in the red marrow is increased, because, apparently, the anæmic condition causes a diminution in the oxygen-supply to the hematopoietic tissue,

<sup>1</sup> Howell: "Life History of the Blood-corpuscles," etc., *Journal of Morphology*, 1890, vol. iv.

<sup>2</sup> *La Semaine médicale*, 1890, p. 464.

<sup>3</sup> *Archiv für exp. Pathol. u. Pharmacol.*, 1897, Bd. 39, S. 426-464.

and thereby stimulates the erythroblastic cells to more rapid multiplication. In the case of a diminution in oxygen-pressure, as happens when the altitude is markedly increased, we may suppose that one result is again a slight diminution in the oxygen-supply to the tissues, including the red marrow, and in consequence the erythroblasts are again stimulated to greater activity. This variation in hæmoglobin with the altitude is an interesting adaptation which ensures always a normal oxygen-capacity for the blood.

**Physiology of the Blood-leucocytes.**—The function of the blood-leucocytes has been the subject of numerous investigations, particularly in connection with the pathology of blood diseases. Although many hypotheses have been made as the result of this work, it cannot be said that we possess any positive information as to the normal function of these cells in the body. It must be borne in mind in the first place that the blood-leucocytes are not all the same histologically, and it may be that their functions are as diverse as is their morphology. Various classifications have been made, based upon one or another difference in microscopic structure and reaction. Thus, Ehrlich groups the leuco-



FIG. 7.—Blood stained with Ehrlich's "triple stain" of acid-fuchsin, methyl-green, and orange G. (drawn with the camera lucida from normal blood) (after Osler): *a*, red corpuscles; *b*, lymphocytes; *c*, large mononuclear leucocytes; *d*, transitional forms; *e*, neutrophilic leucocytes with polymorphous nuclei (polynuclear neutrophiles); *f*, eosinophilic leucocytes.

cytes according to the size, the solubility, and the staining of the granules contained in the cytoplasm, making in the latter respect three main groups; *oxyphiles* or *eosinophiles*, those whose granules stain only with acid aniline dyes—that is, with dyes in which the acid part of the dye acts as the stain; *basophiles*, those which stain only with basic dyes; and *neutrophiles*, those which stain only with neutral dyes<sup>1</sup> (Fig. 7). This classification is frequently used, especially in pathological literature, but it is not altogether satisfactory, since no definite functional relationship of the granules has been established; and, moreover, it is undecided whether or not the granules are permanent or temporary structures in the cells. A simpler classification

<sup>1</sup> Ehrlich: *Die Anämie*, Vienna, 1898; Kanthack and Hardy, *Journal of Physiology*, vol., xvii., 1894, p. 81.



based on morphological characteristics is the following: 1. *Lymphocytes*, which are small corpuscles with a round vesicular nucleus and very scanty cytoplasm; they are not capable of amœboid movements. These corpuscles are so called because they resemble the leucocytes found in the lymph-glands, and are supposed in fact to be brought into the blood through the lymph. According to Ehrlich, they form from 22 to 25 per cent. of the total number of leucocytes. 2. *Mononuclear leucocytes*, which are large corpuscles with a vesicular nucleus and abundant cytoplasm: they have the power of making amœboid movements and are present in only small numbers, 1 per cent. 3. *Polymorphous or polynucleated leucocytes*, which are large corpuscles with the nucleus divided into lobes that are either entirely separated or are connected by fine protoplasmic threads. This form shows active amœboid movements and constitutes the largest proportion of the blood leucocytes, 70 to 72 per cent. 4. The *eosinophile cells*, similar in general to the last, except that the cytoplasm contains numerous coarse granules that take acid stains (eosin) readily. They are present in small numbers, 2 to 4 per cent.

It is impossible to say whether these varieties of blood-leucocytes are distinct histological units that have independent origins and more or less dissimilar functions, or whether, as seems more probable to the writer, they represent different stages in the development of a single type of cell, the lymphocytes forming the youngest and the polymorphic or polynucleated leucocytes the oldest stage. Perhaps the most striking property of the leucocytes as a class is their power of making amœboid movements—a characteristic which has gained for them the sobriquet of “wandering” cells. By virtue of this property some of them are able to migrate through the walls of blood-capillaries into the surrounding tissues. This process of migration takes place normally, but is vastly accelerated under pathological conditions. As to the function or functions fulfilled by the leucocytes, numerous suggestions have been made, some of which may be stated in brief form as follows: (1) They protect the body from pathogenic bacteria. In explanation of this action it has been suggested that they may either ingest the bacteria, and thus destroy them directly, or they may form certain substances, defensive proteids, that destroy the bacteria. Leucocytes that act by ingesting the bacteria are spoken of as “phagocytes” (*φάγειν*, to eat; *κύτος*, cell). This theory of their function is usually designated as the “phagocytosis theory of Metschnikoff;” it is founded upon the fact that the amœboid leucocytes are known to ingest foreign particles with which they come in contact. The theory of the protective action of leucocytes has been used largely in pathology to explain immunity from infectious diseases, and for details of experiments in support of it reference must be made to pathological text-books. (2) They aid in the absorption of fats from the intestine. (3) They aid in the absorption of peptones from the intestine. It may be noticed here that these theories apply to the leucocytes found so abundantly in the lymphoid tissue of the alimentary canal, rather than to those contained in the blood itself. (4) They take part in the process of blood-coagulation. A complete statement with reference to this function must be reserved until the phenomenon of coagulation is

described. (5) They help to maintain the normal composition of the blood-plasma as to its proteids. It may be said for this view that there is considerable evidence to show that the leucocytes normally undergo disintegration and dissolution in the circulating blood, to some extent at least. The blood-proteids are peculiar, and they are not formed directly from the digested food. It is possible that the leucocytes, which are the only typical cells in the blood, aid in keeping up the normal supply of proteids. From this standpoint they might be regarded in fact as unicellular glands, the products of their metabolism serving to maintain the normal composition of the blood-plasma. The formation of granules within the substance of the eosinophiles offers a suggestive analogy to the accumulation of zymogen granules in glandular cells. As to the origin of the leucocytes, it is known that they increase in number while in the circulation, undergoing multiplication by karyokinesis; but the greater number are probably produced in the lymph-glands and in the lymphoid tissue of the body, whence they get into the lymph-stream and eventually are brought into the blood.

**Physiology of the Blood-plates.**—The blood-plates are small circular or elliptical bodies, nearly homogeneous in structure and variable in size ( $0.5$  to  $5.5\mu$ ), but they are always smaller than the red corpuscles (see Histology). Less is known of their origin, fate, and functions than in the case of the leucocytes. It is certain that they are not independent cells, and it is altogether probable, therefore, that they soon disintegrate and dissolve in the plasma. When removed from the circulating blood they are known to disintegrate very rapidly. This peculiarity, in fact, prevented them from being discovered for a long time after the blood had been studied microscopically. Recent work has shown that they are *formed* elements, and not simply precipitates from the plasma, as was suggested at one time. The theory of Hayem, their real discoverer, that they develop into red corpuscles may also be considered as erroneous. There is considerable evidence to show that in shed blood they take part in the process of coagulation. The nature of this evidence will be described later.

Lilienfeld<sup>1</sup> has claimed that chemically the blood-plates contain a nucleo-albumin (see section on Chemistry of the Body), to which he gives the specific name of "nucleohiston." The same substance is contained in the nuclei of leucocytes. This latter fact may be taken as additional evidence for a view which has already been supported on morphological grounds—that the blood-plates are derived from the nuclei of the leucocytes. According to this theory when the polynuclear leucocytes go to pieces in the blood the fragments of nuclei contained in them persist for a longer or shorter time as blood-plates, that in time eventually dissolve in the plasma. If this last statement is correct, then it follows that the substance contained in the blood-plates either goes to form one of the normal constituents of the plasma, useful in nutrition or otherwise, or that it forms a waste product that is eliminated from the body.

<sup>1</sup> *Du Bois-Reymond's Archiv für Physiologie*, 1893, S. 560.



### B. CHEMICAL COMPOSITION OF THE BLOOD; COAGULATION; TOTAL QUANTITY OF BLOOD; REGENERATION AFTER HEMORRHAGE.

**Composition of the Plasma and Corpuscles.**—Blood (plasma and corpuscles) contains a great variety of substances, as may be inferred from its double relations to the tissues as a source of food-supply and as a means of removing the waste products of their functional activity. The constituents existing in quantities sufficiently large for recognition by chemical means are as follows: (1) Water; (2) proteids, of which three varieties at least are known to exist in the plasma—namely, fibrinogen, paraglobulin (serum-globulin), and serum-albumin; (3) combined proteids (hæmoglobin, nucleo-albumins); (4) extractives, including such substances as fats, sugar, urea, lecithin, cholesterin, etc.; and (5) inorganic salts. The proportions of these substances found in the blood of various mammals differ somewhat, although the qualitative composition is practically the same in all.

The following tables, taken from different sources, summarize the general results of the quantitative analyses made by several observers:

*Analysis of the Whole Blood, Human (C. Schmidt).*

	Man (25 years).	Woman (30 years.)
Water . . . . .	788.71	824.55
Solids . . . . .	211.29	175.45
Proteids and extractives . . . . .	191.78	157.93
Fibrin (derived from the fibrinogen) . . . . .	3.93	1.91
Hæmatin (and iron) . . . . .	7.70	6.99
Salts . . . . .	7.88	8.62

*Inorganic Salts of Human Blood, 1000 parts (C. Schmidt).*

Blood-corpuscles.	Blood-plasma.
Cl . . . . . 1.75	Cl . . . . . 3.536
K <sub>2</sub> O . . . . . 3.091	K <sub>2</sub> O . . . . . 0.314
Na <sub>2</sub> O . . . . . 0.470	Na <sub>2</sub> O . . . . . 3.410
SO <sub>3</sub> . . . . . 0.061	SO <sub>3</sub> . . . . . 0.129
P <sub>2</sub> O <sub>5</sub> . . . . . 1.355	P <sub>2</sub> O <sub>5</sub> . . . . . 0.145
CaO . . . . .	CaO . . . . .
MgO . . . . .	MgO . . . . .

These acids and bases exist, of course, in the plasma and the corpuscles as salts. It is not possible to determine exactly how they are combined as salts, but Schmidt suggests the following probable combinations:

Probable Salts in the Corpuscles.	Probable Salts in the Plasma.
Potassium sulphate . . . . . 0.132	Potassium sulphate . . . . . 0.281
Potassium chloride . . . . . 3.679	Potassium chloride . . . . . 0.359
Potassium phosphate . . . . . 2.343	Sodium chloride . . . . . 5.546
Sodium phosphate . . . . . 0.633	Sodium phosphate . . . . . 0.271
Sodium carbonate . . . . . 0.341	Sodium carbonate . . . . . 1.532
Calcium phosphate . . . . . 0.094	Calcium phosphate . . . . . 0.298
Magnesium phosphate . . . . . 0.060	Magnesium phosphate . . . . . 0.218

One interesting fact brought out in the above table is the peculiarity in distribution of the potassium and sodium salts between the plasma and the corpuscles. The plasma contains an excess of the total sodium salts, and the corpuscles contain an excess of the potassium salts.

Composition of Blood-plasma (1000 parts). <sup>1</sup>		Composition of Blood-serum (1000 parts). <sup>1</sup>		
	Horse.	Horse.	Man.	Ox.
Water . . . . .	917.6			
Solids . . . . .	82.4	85.97	92.07	82.63
Total proteids . . . . .	69.5	72.57	76.20	74.99
Fibrin (derived from the fibrinogen)	6.5			
Paraglobulin . . . . .	38.4	45.65	31.04	41.69
Serum-albumin . . . . .	24.6	26.92	45.16	33.30
Extractives and salts . . . . .	12.9	13.40	15.88	14.65

*Red Corpuscles, Human Blood (Hoppe-Seyler).*

	I.	II.
Oxyhæmoglobin . . . . .	86.8	94.3 per cent.
Proteid (and nuclein?) . . . . .	12.2	5.1 "
Lecithin . . . . .	0.7	0.4 "
Cholesterin . . . . .	0.3	0.3 "

*Leucocytes, Thymus of Calf (Lilienfeld).*

In the total dry substance of the corpuscles, which was equal to 11.49 per cent., there were contained—

Proteid . . . . .	1.76 per cent.
Leuco-nuclein . . . . .	68.78 "
Histon . . . . .	8.67 "
Lecithin . . . . .	7.51 "
Fat . . . . .	4.02 "
Cholesterin . . . . .	4.40 "
Glycogen . . . . .	0.80 "

The extractives present in the blood vary in amount under different conditions. Average estimates of some of them, given in percentages of the entire blood, have been reported as follows:

Dextrose (grape-sugar) . . . . .	0.117 per cent.
Urea . . . . .	0.016 "
Lecithin . . . . .	0.0844 "
Cholesterin . . . . .	0.041 "

**Proteids of the Blood-plasma.**—The properties and reactions of proteids and the related compounds, as well as a classification of those occurring in the animal body, are described in the section on the Chemistry of the Body. This description should be read before attempting to study the proteids of the plasma and the part they take in coagulation. Three proteids are usually described as existing in the plasma of circulating blood—namely, fibrinogen, paraglobulin, or, as it is sometimes called, "serum-globulin," and serum-albumin. The first two of these proteids, fibrinogen and paraglobulin, belong to the group of globulins, and hence have many properties in common. Serum-albumin belongs to the group of so-called "native albumins" of which egg-albumin constitutes another member.

<sup>1</sup> Hammarsten: *A Text-book of Physiological Chemistry*, 1898 (translated by Mandel).



*Serum-albumin.*—This substance is a typical proteid. It can be obtained readily in crystalline form. Its percentage composition, according to Hammarsten, is as follows: C 53.06, H 6.85, N 16.04, S 1.80, O 22.26.

Its molecular composition, according to Schmiedeberg,<sup>1</sup> may be represented by  $C_{77}H_{1222}N_{21}SO_4$  or some multiple of this formula. Serum-albumin shows the general reactions of the native albumins. One of its most useful reactions is its behavior toward magnesium sulphate. Serum-albumin usually occurs in liquids together with the globulins, as is the case in blood. If such a liquid is thoroughly saturated with solid  $MgSO_4$ , the globulins are precipitated completely, while the albumin is not affected. So far as the blood and similar liquids are concerned, a definition of serum-albumin might be given by saying that it comprises all the proteids not precipitated by  $MgSO_4$ . When its solutions have a neutral or an acid reaction, serum-albumin is precipitated in an insoluble form by heating the solution above a certain degree. Precipitates produced in this way by heating solutions of proteids are spoken of as coagulations—heat coagulations—and the exact temperature at which coagulation occurs is to a certain extent characteristic for each proteid. The temperature of coagulation of serum-albumin is usually given at from 70° to 75° C., but it varies greatly with the conditions. It has been asserted, in fact, that careful heating under proper conditions gives separate coagulations at three different temperatures—namely, 73°, 77°, and 84° C.—indicating the possibility that what is called “serum-albumin” may be a mixture of three proteids. Serum-albumin occurs in blood-plasma and blood-serum, in lymph, and in the different normal and pathological exudations found in the body, such as pericardial liquid, hydrocele fluid, etc. The amount of serum-albumin in the blood varies in different animals, ranging among the mammals from 2.67 per cent. in the horse to 4.52 per cent. in man. In some of the cold-blooded animals it occurs in surprisingly small quantities—0.36 to 0.69 per cent. As to the source or origin of serum-albumin, it is frequently stated that it comes from the digested proteids of the food. It is known that proteid material in the food is not changed at once to serum-albumin during the act of digestion; indeed, it is known that the final product of digestion is a proteid or group of proteids of an entirely different character—namely, peptones and proteoses; but during the act of absorption into the blood these latter bodies are supposed to undergo transformation into serum-albumin. From a physiological standpoint serum-albumin is considered to be the main source of proteid nourishment for the tissues generally. As will be explained in the section on Nutrition, one of the most important requisites in the nutrition of the cells of the body is an adequate supply of proteid material to replace that used up in the chemical changes, the metabolism, of the tissues. Serum-albumin is supposed to furnish a part, at least, of this supply, although as a matter of fact there is no substantial proof that this view is correct. As long as the serum-albumin is in the blood-vessels it is, of course, cut off from the tissues. The cells, however, are bathed directly in lymph,

<sup>1</sup> *Archiv für exper. Pathol. u. Pharmacol.*, 1897, Bd. 39, S. 1.

and this in turn is formed from the plasma of the blood which is transuded, or, according to some physiologists, secreted, through the vessel-walls.

*Paraglobulin*, which belongs to the group of globulins, exhibits the general reactions characteristic of the group. As stated above, it is completely precipitated from its solutions by saturation with  $\text{MgSO}_4$ . It is incompletely precipitated by saturation with common salt ( $\text{NaCl}$ ). In neutral or feebly acid solutions it coagulates upon heating to  $75^\circ \text{C}$ . Hammarsten gives its percentage composition as—C 52.71, H 7.01, N 15.85, S 1.11, O 23.24. Schmiedeberg gives it a molecular composition corresponding to the formula  $\text{C}_{117}\text{H}_{182}\text{N}_{30}\text{SO}_{38} + \frac{1}{2}\text{H}_2\text{O}$ . According to Faust,<sup>1</sup> the precipitate of paraglobulin usually obtained with  $\text{MgSO}_4$  contains a certain amount of an albuminoid body, *glutolin*, which he believes to be a constant constituent of blood-plasma. Paraglobulin occurs in blood, in lymph, and in the normal and pathological exudations. The amount of paraglobulin present in blood varies in different animals. Among the mammalia the amount ranges from 1.78 per cent. in rabbits to 4.56 per cent. in the horse. In human blood it is given at 3.10 per cent., being less in amount, therefore, than the serum-albumin. It will be seen, upon examining the tables of composition of the blood-plasma and blood-serum of the horse (p. 51), that more of this proteid is found in the serum than in the plasma. This result, which is usually considered as being true, is explained by supposing that during coagulation some of the leucocytes disintegrate and part of their substance passes into solution as a globulin identical with or closely resembling paraglobulin. The figures given above show that a considerable amount of paraglobulin is normally present in blood. It is reasonable to suppose that, like serum-albumin, this proteid is valuable as a source of nitrogenous food to the tissues. It is uncertain, however, whether it is used by the tissues directly as paraglobulin or is first converted into some other form of proteid. It is entirely unknown, also, whether its value as a proteid supply is in any way different from that of serum-albumin. The origin of paraglobulin remains undetermined. It may arise from the digested proteids absorbed from the alimentary canal, but there is no evidence to support such a view. Another suggestion is that it comes from the disintegration of the leucocytes (and other formed elements) of the blood. These bodies are known to contain a small quantity of a globulin resembling paraglobulin, and it is possible that this globulin may be liberated after the dissolution of the leucocytes in the plasma, and thus go to make up the normal supply of paraglobulin. The fact remains, however, that at present the origin and the special use of the paraglobulin are entirely unknown.

*Fibrinogen* is a proteid belonging to the globulin class and exhibiting all the general reactions of this group. It is distinguished from paraglobulin by a number of special reactions; for example, its temperature of heat coagulation is much lower ( $56^\circ$  to  $60^\circ \text{C}$ .), and it is completely thrown down from its solutions by saturation with  $\text{NaCl}$  as well as with  $\text{MgSO}_4$ . Its most important and distinctive reaction is, however, that under proper conditions it gives

<sup>1</sup> Faust, Inaugural Dissertation, Leipzig, 1898.



rise to an insoluble proteid, fibrin, whose formation is the essential phenomenon in the coagulation of blood. Fibrinogen has a percentage composition, according to Hammarsten, of—C 52.93, H 6.90, N 16.66, S 1.25, O 22.26; while its molecular composition, according to Schmiedeberg, is indicated by the formula  $C_{108}H_{162}N_{39}SO_{31}$ .

Fibrinogen is found in blood-plasma, lymph, and in some cases, though not always, in the normal and pathological exudations. It is absent from blood-serum, being used up during the process of clotting. It occurs in very small quantities in blood, compared with the other proteids. There is no good method of determining quantitatively the amount of fibrinogen, but estimates of the amount of fibrin, which cannot differ very much from the fibrinogen, show that in human blood it varies from 0.22 to 0.4 per cent. In horse's blood it may be more abundant—0.65 per cent. As to the origin and the special physiological value of this proteid we are, if possible, more in the dark than in the case of paraglobulin, with the exception that fibrinogen is known to be the source of the fibrin of the blood. But clotting is an occasional phenomenon only. What nutritive function, if any, is possessed by fibrinogen under normal conditions is unknown. No satisfactory account has been given of its origin. It has been suggested by different investigators that it may come from the nuclei of disintegrating leucocytes (and blood-plates) or from the dissolution of the extruded nuclei of newly-made red corpuscles, but here again we have only speculations, that cannot be accepted until some experimental proof is advanced to support them.

**Coagulation of Blood.**—One of the most striking properties of blood is its power of clotting or coagulating shortly after it escapes from the blood-vessels. The general changes in the blood during this process are easily followed. At first shed blood is perfectly fluid, but in a few minutes it becomes viscous and then sets into a soft jelly which quickly becomes firmer, so that the vessel containing it can be inverted without spilling the blood. The clot continues to grow more compact and gradually shrinks in volume, pressing out a smaller or larger quantity of a clear, faintly yellow liquid to which the name *blood-serum* has been given. The essential part of the clot is the fibrin. Fibrin is an insoluble proteid that is absent from normal blood. In shed blood, and under certain conditions in blood while still in the blood-vessels, this fibrin is formed from the soluble fibrinogen. The deposition of the fibrin is peculiar. It is precipitated, if the word may be used, in the form of an exceedingly fine network of delicate threads that permeate the whole mass of the blood and give the clot its jelly-like character. The shrinking of the threads causes the subsequent contraction of the clot. If the blood has not been shaken during the act of clotting, almost all the red corpuscles are caught in the fine fibrin meshwork, and as the clot shrinks these corpuscles are held more firmly, only the clear liquid of the blood being squeezed out, so that it is possible to get specimens of serum containing few or no red corpuscles. The leucocytes, on the contrary, although they are also caught at first in the forming meshwork of fibrin, may readily pass out into the serum in the later stages of clot-

ting, on account of their power of making amœboid movements. If the blood has been agitated during the process of clotting, the delicate network will be broken in places and the serum will be more or less bloody—that is, it will contain numerous red corpuscles. If during the time of clotting the blood is vigorously whipped with a bundle of fine rods, all the fibrin will be deposited as a stringy mass upon the whip, and the remaining liquid part will consist of serum plus the blood-corpuscles. Blood that has been whipped in this way is known as “defibrinated blood.” It resembles normal blood in appearance, but is different in its composition: it cannot clot again. The way in which the fibrin is normally deposited may be demonstrated most beautifully under the microscope by placing a good-sized drop of blood on a slide, covering it with a cover-slip, and allowing it to stand for several minutes until coagulation is completed. If the drop is now examined, it is possible by careful focussing to discover in the spaces between the masses of corpuscles many examples of the delicate fibrin network. The physiological value of clotting is that it stops hemorrhages by closing the openings of the wounded blood-vessels.

*Time of Clotting.*—The time necessary for the clot to form varies slightly in different individuals, or in the blood of the same individual varies with the conditions. It may be said in general that under normal conditions the blood passes into the jelly stage in from three to ten minutes. The separation of clot and serum takes place gradually, but is usually completed in from ten to forty-eight hours. The time of clotting shows marked variations in different animals; the process is especially slow in the horse and the terrapin, so that coagulation of shed blood is more easily prevented in these animals. In the human being also the time of clotting may be much prolonged under certain conditions—in fevers, for example. This fact was noticed in the days when bloodletting was a common practice. The slow clotting of the blood permitted the red corpuscles to sink somewhat, so that the upper part of the clot in such cases was of a lighter color, forming what was called the “buffy coat.” The time of clotting may be shortened or be prolonged, or the clotting may be prevented altogether, in various ways, and much use has been made of this fact in studying the composition and the coagulation of blood as well as in controlling hemorrhages. It will be advantageous to postpone an account of these methods for hastening or retarding coagulation until the theories of coagulation have been considered.

*Theories of Coagulation.*—The clotting of blood is such a prominent phenomenon that it has attracted attention at all times, and as a result numerous theories to account for it have been advanced. Most of these theories possess simply an historical interest, and need not be discussed in a work of this character, but some reference to older views is unavoidable for a proper presentation of the subject. To prevent misunderstanding it may be stated explicitly in the beginning that there is at present no perfectly satisfactory theory. Indeed, the subject is a difficult one, as it is intimately connected with the chemistry of the proteids of the blood, and it may be said that a complete understanding



of clotting waits upon a better knowledge of the nature of these proteids. It is possible that at any moment new facts may be discovered that will alter present ideas of the nature of the process. In considering the different theories that have been proposed there are two general facts that should always be kept in mind: first, that the main phenomenon that a theory of coagulation has to explain is the formation of fibrin; second, that all theories unite in the common belief that the fibrin is derived, in part, at least, from the fibrinogen of the plasma.

*Schmidt's Older Theory of Coagulation.*—The first theory that gained general acceptance in recent times was that of Alexander Schmidt. It was proposed in 1861, and it has served as the basis for all subsequent theories. Schmidt held that the fibrin of the clot is formed by a reaction between paraglobulin (he called it "fibrinoplastin") and fibrinogen, and that this reaction is brought about by a third body, to which he gave the name of *fibrin ferment*. Fibrin ferment was believed to be absent from normal blood, but to be formed after the blood was shed. Further reference will presently be made to the nature of this substance. Schmidt was not able to determine its nature—whether it was a proteid or not—but he discovered a method of preparing it from blood-serum, and demonstrated that it cannot be obtained from blood immediately after it leaves the blood-vessels, and that consequently it does not exist in circulating blood, in any appreciable quantity at least. Finally, Schmidt believed that a certain quantity of soluble salts is necessary as a fourth "fibrin factor."

*Hammarsten's Theory of Coagulation.*—Hammarsten, who repeated Schmidt's experiments, demonstrated that paraglobulin is unnecessary for the formation of fibrin. He showed that if a solution of pure fibrinogen is prepared, and if there is added to it a solution of fibrin ferment entirely free from paraglobulin, a typical clot is formed. This experiment has since been confirmed by others, so that at present it is generally accepted that paraglobulin takes no direct part in the formation of fibrin. Hammarsten's theory was that there are two fibrin factors, fibrin ferment and fibrinogen, and that fibrin results from a reaction between these two bodies. The nature of this reaction could not be determined, but Hammarsten showed that the entire fibrinogen molecule is not changed to fibrin. In place of the fibrinogen there is present after clotting, on the one hand, fibrin representing most of the weight of fibrinogen (60–90 per cent.), and, on the other hand, a newly-formed globulin-like proteid retained in solution in the serum, to which proteid the name *fibrin-globulin* has been given. Hammarsten supposed that although paraglobulin took no direct part in the process, it acted as a favoring condition, a greater quantity of fibrin being formed when it was present. Later experiments<sup>1</sup> indicated that this supposition was incorrect, and that paraglobulin may be eliminated entirely from the theory. The theory of Hammarsten, which is perhaps generally accepted at the present time, is incomplete, however, in that it leaves undetermined the nature of the ferment

<sup>1</sup> Frederikse: *Zeitschrift für physiologische Chemie*, Bd. 19, 1914, S. 143.

and of the reaction between it and fibrinogen. The aim of the newer theories has been to supply this deficiency.

*Schmidt's Theory of Coagulation.*—In a volume<sup>1</sup> containing the results of a lifetime of work devoted to the study of blood-coagulation, Schmidt has modified his well-known theory. His present ideas of the direct and indirect connection of the proteids of the plasma with the formation of fibrin are too complex to be stated clearly in brief compass. He classifies the conditions necessary for coagulation as follows: (1) Certain soluble proteids—namely, the two globulins of the blood—as the material from which fibrin is made. Schmidt does not believe, however, that paraglobulin and fibrinogen react to make fibrin, but believes that fibrinogen is formed from paraglobulin, and that fibrinogen in turn is changed to fibrin. (2) A specific ferment, fibrin ferment, to effect the changes in the proteids just stated. He proposes for fibrin ferment the distinctive name of *thrombin*. (3) A certain quantity of neutral salts is necessary for the precipitation of the fibrin in an insoluble form.

*The Relation of Calcium Salts to Coagulation.*—It has been shown by a number of observers that calcium salts take an important part in the process of clotting. This fact was first clearly demonstrated by Arthus and Pages, who found that if oxalate of potash or soda is added to freshly-drawn blood in quantities sufficient to precipitate the calcium salts, clotting will be prevented. If, however, a soluble calcium salt is again added, clotting occurs promptly. This fact has been demonstrated not only for the blood, but also for pure solutions of fibrinogen, and we are justified in saying that without the presence of calcium salts fibrin cannot be formed from fibrinogen. This is one of the most significant facts recently brought out in connection with coagulation. We know that fibrinogen when acted upon by fibrin ferment produces fibrin, but we now know also that calcium salts must be present. What is the relation of these salts to the so-called “ferment”? The most explicit theory proposed in answer to this question we owe to Pekelharing.

*Pekelharing's Theory of Coagulation.*—Pekelharing<sup>2</sup> succeeded in separating from blood-plasma a proteid body that has the properties of a nucleo-albumin. He finds that if this substance is brought into solution together with fibrinogen and calcium salts, a typical clot will form, while nucleo-albumin alone, or calcium salts alone, added to fibrinogen solutions, cause no clotting. His theory of coagulation is that what has been called “fibrin ferment” is a compound of nucleo-albumin and calcium, and that when this compound is brought into contact with fibrinogen a reaction occurs, the calcium passing over to the fibrinogen and forming an insoluble calcium compound, fibrin. According to this theory, fibrin is a calcium compound with fibrinogen or with a part of the fibrinogen molecule. This idea is strengthened by the unusually large percentage of calcium found in fibrin ash. The theory supposes also that the fibrin ferment is not present in blood-plasma—that is, in sufficient quantity to set up coagulation—but that it is formed

<sup>1</sup> *Zur Blutlehre*, Leipzig, 1893.

<sup>2</sup> *Untersuchungen über das Fibrinferment*, Amsterdam, 1892.



after the blood is shed. The nucleo-albumin part is derived from the corpuscles of the blood (leucocytes, blood-plates), which break down and go into solution. This nucleo-albumin then unites with the calcium salts present in the blood to form fibrin ferment, an organic compound of calcium capable of reacting with fibrinogen. The theory is a simple one; it accounts for the importance of calcium salts in coagulation, and reduces the interchange between fibrinogen and fibrin ferment to the nature of an ordinary chemical reaction; but it cannot be accepted without reservation at present, since the experimental evidence is not entirely in its favor. Hammarsten, for instance, in some careful experiments seems to have obtained facts that are at variance with a part at least of this theory. Hammarsten<sup>1</sup> states that blood-plasma or fibrinogen solutions to which an excess of potassium oxalate had been added, and which therefore was free presumably from precipitable calcium salts, underwent typical coagulation when mixed with blood-serum to which an excess of oxalate had also been added. In other words, a solution of fibrinogen free from calcium reacted with a solution of fibrin ferment (blood-serum) also apparently free from calcium. It might be urged against this experiment, however, that in the blood-serum used the combination of calcium and nucleo-proteid to form ferment had already taken place, and that in this combination the calcium is not acted upon by the oxalate. Hammarsten indeed admits that something of this kind may occur, for he is convinced, like others, that calcium in some way is essential to coagulation, his suggestion being that it plays an unknown part in the formation of the ferment. He supposes that in the plasma of shed blood a material is present which he designates as prothrombin, and the calcium in some way converts this into the active ferment, the thrombin. According to the more explicit hypothesis of Pekelharing, the prothrombin is a form of nucleo-proteid and the thrombin a calcium compound of this proteid. The second part of Pekelharing's theory, namely, that the reaction between the ferment and the fibrinogen consists in a transfer of the calcium from the former to the latter, is directly contradicted by Hammarsten's experiments. Quantitative analysis of fibrinogen and fibrin showed that the latter does not contain any larger amount of calcium than the former. This author is inclined to consider the Ca contained in fibrin of the nature of an impurity, and not as an essential constituent of the fibrin molecule. By the use of special methods he has succeeded in obtaining typical fibrin containing as little as 0.005 per cent. of Ca. We must be content to say that in the clotting of blood three factors are necessary—namely, the fibrinogen and the calcium salts of plasma, which are present in the circulating blood, and the fibrin ferment, which is formed after the blood is shed.

**Nature and Origin of Fibrin Ferment (Thrombin).**—Recent views as to the nature of fibrin ferment have been referred to incidentally in the description of the theories of coagulation just given. The relation of these newer views to the older ideas can be presented most easily by giving a brief description of the development of our knowledge concerning this body.

<sup>1</sup> *Zeitschrift für physiologische Chemie*, Bd. 22, S. 333, and 1899, Bd. 28, S. 98.



Schmidt prepared solutions of fibrin ferment originally by adding a large excess of alcohol to blood-serum and allowing the proteids thus precipitated to stand under strong alcohol for a long time until they were thoroughly coagulated and rendered nearly insoluble in water. At the end of the proper period the coagulated proteids were extracted with water, and there was obtained a solution which contained only small quantities of proteid. It was found that solutions prepared in this way had a marked effect in inducing coagulation when added to liquids, such as hydrocele liquid, that contained fibrinogen, but did not clot spontaneously or else clotted very slowly. It was afterward shown that similar solutions of fibrin ferment are capable of setting up coagulation very readily in so-called salted plasma—that is, in blood-plasma prevented from clotting by the addition of a certain quantity of neutral salts. It was not possible to say whether the coagulating power of these solutions was due to the small traces of proteid contained in them, or whether the proteid was merely an impurity. The general belief for a time, however, was that the proteids present were not the active agent, and that there was in solution something of an unknown chemical nature which acted upon the fibrinogen after the manner of unorganized ferments. This belief was founded mainly upon three facts: first, that the substance seemed to be able to act powerfully upon fibrinogen, although present in such minute quantities that it could not be isolated satisfactorily; second, it was destroyed by heating its solutions for a few minutes at 60° C.; and, third, it did not seem to be destroyed in the reaction of coagulation which it set up, since it was always present in the serum squeezed out of the clot. Schmidt proved that fibrin ferment could not be obtained from blood by the method described above if the blood was made to flow immediately from the cut artery into the alcohol. On the other hand, if the shed blood was allowed to stand, the quantity of fibrin ferment increased up to the time of coagulation, and was present in quantity in the serum. Schmidt believed that the ferment was formed in shed blood from the disintegration of the leucocytes, and this belief was corroborated by subsequent histological work. It was shown in microscopic preparations of coagulated blood that the fibrin threads often radiated from broken-down leucocytes—an appearance that seemed to indicate that the leucocytes served as points of origin for the deposition of the fibrin. When the blood-plates were discovered a great deal of microscopic work was done tending to show that these bodies also are connected with coagulation in the same way as the leucocytes, and serve probably as sources of fibrin ferment. In microscopic preparations the fibrin threads were found to radiate from masses of partially disintegrated plates; and, moreover, it was discovered that conditions which retard or prevent coagulation of blood often serve to preserve the delicate plates from disintegration. At the present time it is generally believed that there is derived from the disintegration of the leucocytes and blood-plates something that is necessary to the coagulation of blood, but there is some difference of opinion as to the nature of this substance and whether it is identical with Schmidt's fibrin ferment. Pekelharing thinks that the substance set free from the corpuscles and plates

is a nucleo-proteid, but that this nucleo-proteid is not capable of acting upon fibrinogen until it has combined with the calcium salts of the blood. According to his view, therefore, fibrin ferment, in Schmidt's sense, is a compound of calcium and nucleo-proteid. Lilienfeld has shown by chemical reactions that blood-plates and nuclei of leucocytes contain nucleo-proteid material which in all probability is liberated in the blood-plasma by the disintegration of these elements after the blood is shed. Lilienfeld contends, however, that solutions of fibrin ferment prepared by Schmidt's method do not contain any nucleo-proteid material, and that, although the liberation of nucleo-proteid material is what starts normal coagulation of blood, nevertheless so-called fibrin ferment is something entirely different from nucleo-proteid. In this point, however, his results are contradicted by the experiments of Pekelhar- ing and of Halliburton, who both find that solutions of fibrin ferment prepared by Schmidt's method give distinct evidence of containing nucleo-pro- teid material. We may conclude, therefore, that the essential element of Schmidt's fibrin ferment is a nucleo-proteid compound. The nature of the action of the ferment on fibrinogen is quite undetermined. As was mentioned before, only a portion, and apparently a variable portion, of this fibrinogen appears as fibrin after clotting is completed. Along with the fibrin a new proteid fibrin globulin makes its appearance in the serum. This fact has suggested the view that perhaps the fibrin ferment acts after the manner of the digestive ferments by causing hydrolytic cleavage of the fibrinogen, that is, causes the fibrinogen molecule to take up water and then dissociate into two parts, fibrin and fibrin globulin. Hammarsten, however, is inclined to believe that the reaction is of a different nature, resembling more the change that occurs in the heat coagulation of proteids. According to this suggestion, the ferment causes a molecular rearrangement of the fibrinogen, resulting in the formation of fibrin, most of which is deposited in an insoluble form, while a smaller part, after suffering a still further alteration, appears as fibrin globulin.

**Intravascular Clotting.**—Clotting may be induced within the blood- vessels by the introduction of foreign particles, either solid or gaseous—for example, air—or by injuring the inner coat of the blood-vessels, as in ligat- ing. In the latter case the area injured by the ligature acts as a foreign surface and probably causes the disintegration of a number of corpuscles. The clot in this case is confined at first to the injured area, and is known as a "thrombus." Intravascular clotting more or less general in occurrence may be produced by injecting into the circulation such substances as leucocytes obtained by macerating lymph-glands, extracts of fibrin ferment, solutions of nucleo-albumins of different kinds, etc. According to the theory of coagu- lation adopted above, injections of these latter substances ought to cause coagu- lation very readily, since the blood already contains fibrinogen, and needs only the presence of ferment to set up coagulation. As a matter of fact, however, intravascular clotting is produced with some difficulty by these methods, show- ing that the body can protect itself within certain limits from an excess of



ferment in the circulating blood. Just how this is done is not positively known, but there is evidence that it may be due mainly to a defensive action of the liver. Delezenne<sup>1</sup> states that when blood-serum is circulated through a liver it loses its power of inducing coagulation in a coagulable liquid, that is, probably its contained fibrin ferment is altered or destroyed. It seems probable that this action of the liver may be of importance in the normal circulation in maintaining the non-coagulability of the blood in the living animal. Moreover, injection of leucocytes sometimes diminishes instead of increasing the coagulability of blood, making the so-called "negative phase" of the injection. To explain this latter fact, it may be said that leucocytes give rise on disintegration to a complex nucleo-proteid known as nucleo-histon. Nucleo-histon in turn is said to be broken up in the circulation, with the formation of a second nucleo-proteid, leuconuclein, that favors coagulation, and a proteid body, histon, that has a retarding influence on coagulation. The predominance of the latter substance may account for the "negative phase" under the conditions described.

**Why Blood does not Clot within the Blood-vessels.**—The reason that blood remains fluid while in the living blood-vessels, but clots quickly after being shed or after being brought into contact with a foreign substance in any way, has already been stated in describing the theories of coagulation, but will be restated here in more categorical form. Briefly, then, blood does not clot within the blood-vessels because fibrin-ferment is not present in sufficient quantities at any one time. Leucocytes and blood-plates probably disintegrate here and there within the circulation, but the small amount of ferment thus formed is insufficient to act upon the blood, and the ferment is quickly destroyed or changed, probably by an action of the liver as stated above. When blood is shed, however, the formed elements break down in mass, as it were, liberating a relatively large amount of nucleo-proteids, which, together with the calcium salts, produce fibrin from the fibrinogen.

**Means of Hastening or of Retarding Coagulation.**—Blood coagulates normally within a few minutes, but the process may be hastened by increasing the extent of foreign surface with which it comes in contact. Thus, moving the liquid when in quantity, or the application of a sponge or a handkerchief to a wound, will hasten the onset of clotting. This is easily understood when it is remembered that nucleo-proteids arise from the breaking down of leucocytes and blood-plates, and that these corpuscles go to pieces more rapidly when in contact with a dead surface. It has been proposed also to hasten clotting in case of hemorrhage by the use of ferment solutions. Hot sponges or cloths applied to a wound will hasten clotting, probably by accelerating the formation of ferment and the chemical changes of clotting. Coagulation may be retarded or be prevented altogether by a variety of means, of which the following are the most important:

1. *By Cooling.*—This method succeeds well only in blood that clots slowly—for example, the blood of the horse or the terrapin. Blood from

<sup>1</sup> *Travaux de Physiologie*, Université de Montpellier, 1898.



these animals received into narrow vessels surrounded by crushed ice may be kept fluid for an indefinite time. The blood-corpuscles soon sink, so that this method is an excellent one for obtaining pure blood-plasma. The cooling probably prevents clotting by keeping the corpuscles intact.

2. *By the Action of Neutral Salts.*—Blood received at once from the blood-vessels into a solution of such neutral salts as sodium sulphate or magnesium sulphate, and well mixed, will not clot. In this case also the corpuscles settle slowly, or they may be centrifugalized, and specimens of plasma can be obtained. For this purpose horse's or cat's blood is to be preferred. Such plasma is known as "salted plasma;" it is frequently used in experiments in coagulation—for example, in testing the efficacy of a given ferment solution. The best salt to use is  $MgSO_4$  in solutions of 27 per cent.: 1 part by volume of this solution is usually mixed with 4 parts of blood; if cat's blood is used a smaller amount may be taken—1 part of the solution to 9 of blood. Salted plasma or salted blood again clots when diluted sufficiently with water or when ferment solutions are added to it. How the salts prevent coagulation is not definitely known—possibly by preventing the disintegration of corpuscles and the formation of ferment, possibly by altering the chemical properties of the proteids.

3. *By the Action of Albumose Solutions.*—Certain of the products of proteid digestion, peptones and albumoses, when injected into the circulation retard clotting for a long time. For injection into dogs one uses 0.3 gram to each kilogram of animal. If the blood is withdrawn shortly after the injection, it will remain fluid for a long time. The peptone solutions, on the contrary, have no effect on the clotting of blood if added to it in a glass outside the body. This curious action of peptone has been much discussed. In an interesting paper by Delezenne, referred to on the previous page, two important facts are brought out that furnish the author a basis for a credible theory of the anticoagulating effect of the injections. It has been shown, in the first place, that the peptone injections cause a marked and rapid destruction of blood leucocytes. Secondly, that if blood and peptone are circulated together through a living liver the mixture not only does not clot itself, but will prevent clotting when added to freshly drawn blood. The hypothesis to explain these facts and also the action of peptone on coagulation is that the peptone by destroying the leucocytes sets free nucleo-proteid and histon (see p. 61); the former of these by forming fibrin ferment would promote coagulation, but in passing through the liver it is destroyed or neutralized in some way, and the histon left in the blood is the substance that retards the clotting. It would be desirable, in connection with this hypothesis, if chemical proof were furnished that histon is present in the blood after peptone injections.

4. Many other organic substances have an effect similar to peptone when injected into the circulation or in some cases when mixed with shed blood. For example, extracts of leech's head, extracts of the muscle of the crayfish, the serum of the eel, a number of bacterial toxins, and many of the soluble

enzymes such as pepsin, trypsin, diastase, etc. The hypothesis used to explain the action of peptone may possibly apply also to these cases.

5. *By the Action of Oxalate Solutions.*—If blood as it flows from the vessels is mixed with solutions of potassium or sodium oxalate in proportion sufficient to make a total strength of 0.1 per cent. or more of these salts, coagulation will be prevented entirely. Addition of an excess of water will not produce clotting in this case, but solutions of some soluble calcium salt will quickly start the process. The explanation of the action of the oxalate solutions is simple: they are supposed to precipitate the calcium as insoluble calcium oxalate.

**Total Quantity of Blood in the Body.**—The total quantity of blood in the body has been determined approximately for man and a number of the lower animals. The method used in such determinations consists essentially in first bleeding the animal as thoroughly as possible and weighing the quantity of blood thus obtained, and afterward washing out the blood-vessels with water and estimating the amount of hæmoglobin in the washings. The results are as follows: Man, 7.7 per cent. ( $\frac{1}{13}$ ) of the body-weight; that is, a man weighing 68 kilos. has about 5236 grams, or 4965 c.c., of blood in his body; dog, 7.7 per cent.; rabbit and cat, 5 per cent.; new-born human being, 5.26 per cent.; and birds, 10 per cent. Moreover, the distribution of this blood in the tissues of the body at any one time has been estimated by Ranke,<sup>1</sup> from experiments on freshly-killed rabbits, as follows:

Spleen . . . . .	0.23 per cent.
Brain and cord . . . . .	1.24 " "
Kidneys . . . . .	1.63 " "
Skin . . . . .	2.10 " "
Intestines . . . . .	6.30 " "
Bones . . . . .	8.24 " "
Heart, lungs, and great blood-vessels . . . . .	22.76 " "
Resting muscles . . . . .	29.20 " "
Liver . . . . .	29.30 " "

It will be seen from inspection of this table that in the rabbit the blood of the body is distributed at any one time about as follows: one-fourth to the heart, lungs, and great blood-vessels; one-fourth to the liver; one-fourth to the resting muscles; and one-fourth to the remaining organs.

**Regeneration of the Blood after Hemorrhage.**—A large portion of the entire quantity of blood in the body may be lost suddenly by hemorrhage without producing a fatal result. The extent of hemorrhage that can be recovered from safely has been investigated upon a number of animals. Although the results show more or less individual variation, it can be said that in dogs a hemorrhage of from 2 to 3 per cent. of the body-weight<sup>2</sup> is recovered from easily, while a loss of 4.5 per cent., more than half the entire blood, will probably prove fatal. In cats a hemorrhage of from 2 to 3 per

<sup>1</sup> Taken from Vierordt's *Anatomische, physiologische und physikalische Daten und Tabellen*, Jena, 1893.

<sup>2</sup> Fredericq: *Travaux du Laboratoire (Université de Liège)*, 1885, t. i. p. 189.



cent. of the body-weight is not usually followed by a fatal result. Just what percentage of loss can be borne by the human being has not been determined, but it is probable that a healthy individual may recover without serious difficulty from the loss of a quantity of blood amounting to as much as 3 per cent. of the body-weight. It is known that if liquids that are isotonic to the blood, such as a 0.9 per cent. solution of NaCl, are injected into the veins immediately after a severe hemorrhage, recovery will be more certain; in fact, it is possible by this means to restore persons after a hemorrhage that would otherwise have been fatal. In addition to the mechanical effects on blood pressure such an infusion tends to put into circulation all the red corpuscles. Ordinarily the number of red corpuscles is greater than that necessary for a barely sufficient supply of oxygen, and increasing the bulk of liquid in the vessels after a severe hemorrhage makes more effective as oxygen-carriers the remaining red corpuscles, inasmuch as it insures a more rapid circulation. If a hemorrhage has not been fatal, experiments on lower animals show that the plasma of the blood is regenerated with great rapidity, the blood regaining its normal volume within a few hours in slight hemorrhages, and in from twenty-four to forty-eight hours if the loss of blood has been severe; but the number of red corpuscles and the hæmoglobin are regenerated more slowly, getting back to normal only after a number of days or after several weeks.

**Blood-transfusion.**—Shortly after the discovery of the circulation of the blood (Harvey, 1628), the operation was introduced of transfusing blood from one individual to another or from some of the lower animals to man. Extravagant hopes were held as to the value of such transfusion not only as a means of replacing the blood lost by hemorrhage, but also as a cure for various infirmities and diseases. Then and subsequently, fatal as well as successful results followed the operation. It is now known to be a dangerous undertaking, mainly for two reasons: first, the strange blood, whether transfused directly or after defibrination, is liable to contain a quantity of fibrin ferment sufficient to cause intravascular clotting; secondly, the serum of one animal may be toxic to another or cause a destruction of its blood-corpuscles. Owing to this globulicidal and toxic action, which has previously been referred to (p. 36), the injection of foreign blood is likely to be directly injurious instead of beneficial. In cases of loss of blood from severe hemorrhage, therefore, it is far safer to inject a neutral liquid, such as the so-called "physiological salt-solution"—a solution of NaCl of such a strength (0.9 per cent.) as to be isotonic with the blood-serum. The volume of the circulating liquid is thereby augmented, and all the red corpuscles are made more efficient as oxygen-carriers, partly owing to the fact that the bulk and velocity of the circulation are increased, and partly because the corpuscles are kept from stagnation in the capillary areas.



**Some Preliminary Considerations upon the Processes of Diffusion and Osmosis, and their Importance in the Nutritive Exchanges of the Body.**

In recent years the physical conceptions of the nature of the processes of diffusion and osmosis have changed considerably. As these newer conceptions are entering largely into current medical literature, it seems advisable to give a brief description of them for the use of those students of physiology who may be unacquainted with the modern nomenclature. The very limited space that can be devoted to the subject forbids anything more than a condensed elementary presentation. For fuller information reference must be made to special treatises.<sup>1</sup>

*Diffusion, Dialysis, and Osmosis.*—When two gases are brought into contact a homogeneous mixture of the two is soon obtained. This interpenetration of the gases is spoken of as diffusion, and it is due to the continual movements of the gaseous molecules to and fro within the limits of the confining space. So also when two miscible liquids or solutions are brought into contact a diffusion occurs for the same reason, the movements of the molecules finally effecting a homogeneous mixture. If the two liquids happen to be separated by a membrane, diffusion will still occur, provided the membrane is permeable to the liquid molecules, and in time the liquids on the two sides will be mixtures having a uniform composition. Not only water molecules, but the molecules of many substances in solution, such as sugar, may pass to and fro through membranes, so that two liquids separated from each other by an intervening membrane and originally unlike in composition may finally, by the act of diffusion, come to have the same composition. Diffusion of this kind through a membrane is frequently spoken of as dialysis or osmosis. In the body we deal with aqueous solutions of various substances that are separated from each other by living membranes, such as the walls of the blood-capillaries or of the alimentary canal, and the laws of diffusion through membranes are of immediate importance in explaining the passage of water and dissolved substances through these living septa. In aqueous solutions such as we have in the body we must take into account the movements of the molecules of the solvent, water, as well as of the substances dissolved. These latter may have different degrees of diffusibility as compared with one another or with the water molecules, and it frequently happens that a membrane that is permeable to water molecules is less permeable or even impermeable to the molecules of the substances in solution. For this reason the diffusion stream of water and of the dissolved substances may be differentiated, as it were, to a greater or less extent. In recent years it seems to have become customary to limit the term osmosis to the stream of water molecules passing through a membrane, while the term dialysis, or diffusion, is applied to the passage of the molecules of the substances in solution. The osmotic stream of water under varying conditions is especially important, and in connection with this process it is necessary to define the term osmotic pressure as applied to solutions.

*Osmotic Pressure.*—If we imagine two masses of water separated by a permeable membrane, we can readily understand that as many water molecules will pass through from one side as from the other; the two streams in fact will neutralize each other, and the volumes of the two masses of water will remain unchanged. The movement of the water molecules in this case is not actually observed, but it is assumed to take place on the theory that the liquid molecules are continually in motion and that the membrane, being permeable, offers no obstacle to their movements. If, now, on one side of the membrane we place a solution of some crystalloid substance, such as common salt, and on the other side pure water, then it will be found that an excess of water will pass from

<sup>1</sup> Consult: H. C. Jones, *The Theory of Electrolytic Dissociation*, 1900; "Diffusion, Osmosis, and Filtration," by E. W. Reid, in Schäfer's *Text-book of Physiology*, 1898; *Solution and Electrolysis*, by W. C. D. Whetham, Cambridge Natural Science Manuals, 1895.

the water side to the side containing the solution. In the older terminology it was said that the salt attracted this water, but in the newer theories the same fact is expressed by saying that the salt in solution exerts a certain osmotic pressure, in consequence of which more water flows from the water side to the side of the solution than in the reverse direction. As a matter of experiment it is found that the osmotic pressure varies with the amount of the substance in solution. If in experiments of this kind a semi-permeable membrane is chosen—that is, a membrane that is permeable to the water molecules, but not to the molecules of the substance in solution—the stream of water to the side of the crystalloid will continue until the hydrostatic pressure on this side reaches a certain point, and the hydrostatic pressure thus caused may be taken as a measure of the osmotic pressure exerted by the substance in solution. Under these conditions it can be shown that the osmotic pressure is proportional to the concentration of the solution, or, in other words, to the number of molecules and ions of the crystalloid in solution. As a matter of fact it is difficult, if not impossible, to construct membranes that are truly semi-permeable; most of the membranes that we have to use in practice are only approximately semi-permeable—that is, while they are readily permeable to water molecules, they are also permeable, although with more or less difficulty, to the substances in solution. In such cases we get an osmotic stream of water to the side of the dissolved crystalloid, but at the same time the molecules of the latter pass to some extent through the membrane, by diffusion, to the water side. In course of time, therefore, the dissolved crystalloid will be equally distributed on the two sides of the membrane, the osmotic pressure on both sides will become equal, and osmosis of the water will cease to be apparent, since it will be equal in the two directions. All substances in solution are capable of exerting osmotic pressure, and the important discovery has been made that the osmotic pressure, measured in terms of atmospheres or the pressure of a column of water or mercury, is equal to the gas pressure that would be exerted by a number of molecules of gas equal to that of the crystalloid in solution, if confined within the same space and kept at the same temperature. A perfectly satisfactory explanation of the nature of osmotic pressure has not been furnished. We must be content to use the term to express the fact described. A comparatively simple explanation, however, has been suggested, which has the great merit of referring the whole phenomenon to the molecular movements of the solvent and of the substance dissolved—that is, to the same ultimate cause that brings about the entire process of diffusion in liquids. The nature of this explanation may be understood from a simple illustration. Suppose that we have a solution of cane-sugar separated from a mass of water by a semi-permeable membrane—that is, in this case a membrane permeable to the water molecules but not to the sugar molecules. Under these conditions the stream of water from the two sides will be unequal, because on the one side we have water molecules moving against the membrane in what we may call normal numbers, while on the other side both water and sugar molecules may be considered as striking against the membrane. On this side the sugar molecules screen the membrane, as it were, from contact with a certain number of water molecules, and the result follows that in a given unit of time fewer molecules of water will penetrate the membrane from this side than from the other; or, to put it in another way, the osmotic stream of water from the unscreened water side to the sugar side will be greater than in the reverse direction. Upon this hypothesis one can readily see why the osmotic pressure should be proportional to the number of molecules of the crystalloid in the solution—that is, to the concentration of the solution. It is a matter of great importance to measure the osmotic pressures of various solutions. As was stated above, this measurement could be made easily for any solution provided a really semi-permeable membrane could be constructed. As a matter of experience, however, it is possible to make such membranes in only a few cases, and in these cases perhaps the semi-permeability is only approximately complete. In actual experiments other methods must be employed, and a brief statement of a theoretical and a practical method of arriving at the value of osmotic pressures may be of service in further illus-



*Mabrams*

trating the meaning of the term. Before stating these methods it becomes necessary to define two terms, namely, electrolytes and gram-molecular solutions, that are much used in this connection.

*Electrolysis.*—The molecules of many substances when brought into a state of solution are believed to be dissociated into two or more parts, known as ions. The completeness of the dissociation varies with the substance used, and for any one substance with the degree of dilution. Roughly speaking, the greater the dilution the more nearly complete is the dissociation. The ions liberated by this act of dissociation are charged with electricity, and when an electrical current is led into such a solution it is conducted through the solution by the movements of the ions. The molecules of perfectly pure water undergo practically no dissociation, and water therefore does not appreciably conduct the electrical current. If some NaCl is dissolved in water, a certain number of its molecules become dissociated into a Na ion charged positively with electricity and a Cl ion charged negatively, and the solution becomes a conductor of the electrical current. Substances that exhibit this property of dissociation are known as electrolytes, to distinguish them from other soluble substances, such as sugar, that do not dissociate in solution and therefore do not conduct the electrical current. Speaking generally, it may be said that all salts, bases, and acids belong to the group of electrolytes. The conception of electrolytes is very important for the reason that the act of dissociation obviously increases the number of particles moving in the solution and thereby increases the osmotic pressure, since it has been found experimentally that, so far as osmotic pressures are concerned, an ion plays the same part as a molecule. It follows, therefore, that the osmotic pressure of any given electrolyte in solution will be increased in proportion to the degree to which it is dissociated. As the liquids of the body contain electrolytes in solution it becomes necessary in estimating their osmotic pressure to take this fact into consideration.

*Gram-molecular Solutions.*—The concentration of a given substance in solution may be stated by the usual method of percentages, but from the standpoint of osmotic pressure a more convenient method is the use of the unit known as a gram-molecular solution. A gram-molecule of any substance is a quantity in grams of the substance equal to its molecular weight, while a gram-molecular solution is one containing a gram-molecule of the substance to a liter of the solution. Thus a gram-molecular solution of sodium chloride is one containing 58.5 grams (Na 23, Cl 35.5) of the salt to a liter, while a gram-molecular solution of cane-sugar contains 342.1 grams ( $C_{12}H_{22}O_{11}$ ) to a liter. Similarly a gram-molecule of H is 2 grams by weight of this gas, and if this weight of H were compressed to the volume of a liter it would be comparable to a gram-molecular solution. Since the weight of a molecule of H is to the weight of a molecule of cane-sugar as 2 is to 342.1, it follows that a liter containing 2 grams of H contains the same number of molecules of H in it as a liter of solution containing 342.1 grams of sugar has of sugar molecules. Since it is known that a molecule in solution exerts an osmotic pressure that is exactly equal to the gas-pressure exerted by a gas molecule moving in the same space and at the same temperature, we are justified in saying that the osmotic pressure of a gram-molecular solution of cane-sugar, or of any other substance that is not an electrolyte, is equal to the gas-pressure of 2 grams of H when compressed to the volume of 1 liter. This fact gives a means of calculating the osmotic pressure of solutions in certain cases according to the following method:

*Calculation of the Osmotic Pressure of Solutions.*—To illustrate this method we may take a simple problem such as the determination of the osmotic pressure of a 1 per cent. solution of cane-sugar. One gram of H at atmospheric pressure occupies a volume of 11.16 liters; 2 grams of H, therefore, under the same conditions will occupy a volume of 22.32 liters. A gram-molecule of H—that is, 2 grams of H—when brought to the volume of 1 liter will exert a gas-pressure equal to that of 22.32 liters compressed to 1 liter—that is, a pressure of 22.32 atmospheres. A gram-molecular solution of cane-sugar, since it contains the same number of molecules in a liter, must therefore exert an osmotic pressure



equal to 22.32 atmospheres. A 1 per cent. solution of cane sugar contains, however, only 10 grams of sugar to a liter, hence the osmotic pressure of the sugar in such a solution will be  $\frac{10}{342.1}$  of 22.32 atmospheres, or 0.65 of an atmosphere, which in terms of a column of mercury would give  $760 \times 0.65 = 494$  mm. This figure expresses the osmotic pressure of a 1 per cent. solution of cane-sugar when dialyzed against pure water through a membrane impermeable to the sugar molecules. In such an experiment water would pass to the sugar side until the hydrostatic pressure on this side was increased by an amount equal to the pressure of a column of mercury 494 mm. high. Certain additional calculations that it is necessary to make for the temperature of the solution need not be specified in this connection. If, however, we wished to apply this method to the calculation of the osmotic pressure of a given solution of an electrolyte, it would be necessary first to ascertain the degree of dissociation of the electrolyte into its ions, since, as was said above, dissociation increases the number of parts in solution and to the same extent increases osmotic pressure. In the body the liquids that concern us contain a variety of substances in solution, electrolytes as well as non-electrolytes. In order, therefore, to calculate the osmotic pressure of such complex solutions it would be necessary to ascertain the amount of each substance present, and, in the case of electrolytes, the degree of dissociation. Under experimental conditions such a calculation is practically impossible, and recourse must be had to other methods. One of the simplest and most easily applied of these methods is the determination of the freezing-point of the solution.

*Determination of Osmotic Pressure by Means of the Freezing-point.*—This method depends upon the fact that the freezing-point of water is lowered by substances in solution, and it has been discovered that the amount of lowering is proportional to the number of parts (molecules and ions) present in the solution. Since the osmotic pressure is also proportional to the number of parts in solution, it is convenient to take the lowering of the freezing-point of a solution as an index or measure of its osmotic pressure. In practice a simple apparatus (Beckmann's apparatus) is used, consisting essentially of a very delicate and adjustable differential thermometer. By means of this instrument the freezing-point of pure water is first ascertained upon the empirical scale of the thermometer. The freezing-point of the solution under examination is then determined, and the number of degrees or fractions of a degree by which its freezing-point is lower than that of pure water is noted. The lowering of the freezing-point in degrees centigrade is expressed usually by the symbol  $\Delta$ . For example, mammalian blood-serum gives  $\Delta = 0.56^\circ \text{C}$ . A 0.95 per cent. solution of NaCl gives the same  $\Delta$ ; hence the two solutions exert the same osmotic pressure, or, to put it in another way, a 0.95 per cent. solution of NaCl is isotonic or isosmotic with mammalian serum. The  $\Delta$  of any given solution may be expressed in terms of a gram-molecular solution by dividing it by the constant 1.87, since a gram-molecular solution of a non-electrolyte is known to lower the freezing point  $1.87^\circ \text{C}$ . Thus if blood-serum gives  $\Delta = 0.56^\circ \text{C}$ , its concentration in terms of a gram-molecular solution will be  $\frac{0.56}{1.87}$ , or 0.3. In other words, blood-serum has 0.3 of the osmotic pressure exerted by a gram-molecular solution of a non-electrolyte—that is,  $22.32 \times 0.3$ , or 6.696 atmospheres.

*Remarks upon the Application of the Foregoing Facts in Physiology.*—In the body water and substances in solution are continually passing through membranes, for example, in the production of lymph, in the absorption of water and digested food-stuffs from the alimentary canal, in the nutritive exchanges between the tissue-elements and the blood or lymph, in the production of the various secretions, and so on. In these cases it is a matter of the greatest difficulty to give a satisfactory explanation of the forces controlling the flow to and fro of the water and dissolved substances; but there can be little doubt that in all of them the physical forces of filtration, diffusion, and osmosis take an important part. Whatever can be learned therefore concerning these processes must in

the end have an important bearing upon the explanation of the nutritive exchanges between the blood and tissues. Some additional facts may be mentioned to indicate the applications that are made of these processes in explaining physiological phenomena.

*Osmotic Pressure of Proteids.*—The osmotic pressure exerted by crystalloids, such as the ordinary soluble salts, is, as we have seen, very considerable, but the ready diffusibility of most of these salts through animal membranes limits very materially their influence upon the flow of water in the body. Thus if we should inject a strong solution of common salt directly into the blood-vessels, the first effect would be the setting up of an osmotic stream from the tissues to the blood and the production of a condition of hydraemic plethora within the blood-vessels. The salt, however, would soon diffuse out into the tissues, and to the degree that this occurred its effect in diluting the blood would tend to diminish because the part of the salt that got into the extra-vascular lymph-spaces would now exert an osmotic pressure in the opposite direction, drawing water from the blood. This fact, together with the further fact that an excess of salts in the body is soon removed by the excreting organs, gives to such substances a smaller influence in directing the water stream than would at first be supposed when the intensity of their osmotic action is considered. In addition to the crystalloids the liquids of our bodies contain also a certain amount of proteid, the blood, especially, containing over 6 per cent. of this substance. It has been generally assumed that proteids in solution exert little or no osmotic pressure, but Starling<sup>1</sup> and others have claimed, on the contrary, that proteids in solution exert a distinct although small osmotic pressure, and it is probable that this fact is of special importance in absorption because the proteids do not diffuse or diffuse with great difficulty, and their effect remains therefore, so to speak, as a permanent factor. According to Starling, the osmotic pressure exerted by the proteids of serum is equal to about 30 mm. of mercury. That the osmotic pressure of the serum proteids is so small is not surprising if we remember the very high molecular weight of this substance. In serum the proteids are present in a concentration of about 7 per cent., but owing to their large molecular weight comparatively few proteid molecules are present in a solution of this concentration: and assuming that the dissolved proteid follows the laws discovered for crystalloids its osmotic pressure would depend upon the number of molecules in solution. By means of this weak but constant osmotic pressure of the indiffusible proteid it is possible to explain the fact that an isotonic or even a hypertonic solution of diffusible crystalloid may be completely absorbed by the blood from the peritoneal cavity.

*Isotonic, Hypertonic, and Hypotonic Solutions.*—In physiology the osmotic pressures exerted by various solutions are compared usually with that of the blood-serum. In this sense an isotonic or isosmotic solution is one having an osmotic pressure equal to that of serum, a hypertonic or hyperosmotic solution is one whose osmotic pressure exceeds that of serum, and a hypotonic or hyposmotic solution is one whose osmotic pressure is less than that of serum.

*Diffusion, or Dialysis, of Soluble Constituents.*—If two liquids of unequal concentration in a given constituent are separated by a membrane entirely permeable to the dissolved molecules of the substance, a greater number of these molecules will pass over from the more concentrated to the less concentrated side, and in time the composition will be the same on the two sides of the membrane. Diffusion of soluble constituents continually takes place, therefore, from the points of greater concentration to those of less, and this may happen quite independently of the direction of the osmotic stream of water. If, for instance, a 0.9 per cent. solution of sodium chloride is injected into the peritoneal cavity, it will enter into diffusion relations with the blood in the blood-vessels; its concentration in sodium chloride being greater than that of the blood, the excess will tend to pass into the blood, while sodium carbonate, urea, sugar, and other soluble crystalloidal substances will pass from the blood into the salt solution in the peritoneal cavity. Through the action of this process of diffusion we can understand how certain constituents of the blood may pass

<sup>1</sup> *Journal of Physiology*, 1899, vol. 24, p. 317.



to the tissues of various glands in amounts greater than could be explained if we supposed that the lymph of these tissues was derived solely by filtration from the blood-plasma. (See p. 72 for an illustration.) Another important conception in this connection is the possibility that the capillary walls may be permeable in different degrees to the various soluble constituents of the blood, and furthermore the possibility that the permeability of the capillary walls may vary in different organs. With regard to the first possibility it has been shown by Roth<sup>1</sup> that the blood-capillaries are more permeable to the urea molecules than to sugar or NaCl. With the aid of these facts it is possible to explain in large measure the transportation of material from the blood to the tissues, and *vice versa*. For example, to follow a line of reasoning used by Roth, we may suppose that the functional activity of the tissue-elements is attended by a consumption of material which in turn is made good by the dissolved molecules in the tissue-lymph. The concentration of the latter is thereby lowered, and in consequence a diffusion stream of these substances is set up with the more concentrated blood. In this way, by diffusion, a constant supply of dissolved material is kept in motion from the blood to the tissue-elements. On the other hand, the functional activity of the tissue-elements is accompanied by a breaking down of the complex proteid molecule with the formation of simpler, more stable molecules of crystalloid character, such as the sulphates, phosphates, and urea or some precursor of urea. As these bodies pass into the tissue-lymph they tend to increase its molecular concentration, and thus by the greater osmotic pressure which they exert serve to attract water from the blood to the lymph, forming one efficient factor in the production of lymph. On the other hand, as these substances accumulate in the lymph to a concentration greater than that possessed by the same substances in the blood, they will diffuse toward the blood. By this means the waste-products of activity are drawn off to the blood, from which in turn they are removed by the action of the excretory organs.

*Diffusion of Proteids.*—This simple explanation on purely physical grounds of the flow of material between the blood and the tissues can only be applied, however, at present to the diffusible crystalloids, such as the salts, urea, and sugar. The proteids of the blood, which are supposed to be so important for the nutrition of the tissues, are practically indiffusible, so far as we know. It is difficult to explain their passage from the blood through the capillary walls into the lymph. Provisionally it may be assumed that this passage is due to filtration. The blood-plasma in the capillaries is under a slightly higher pressure than the lymph of the tissues, and this higher pressure tends to squeeze the blood-constituents, including the proteid, through the capillary walls. This explanation, however, cannot be said to be satisfactory, and in this respect the purely physical theory of lymph-formation waits upon a clearer knowledge of the nature of the nutritive proteids and their relations to the capillary walls.

## LYMPH.

LYMPH is a colorless liquid found in the lymph-vessels as well as in the extravascular spaces of the body. All the tissue-elements, in fact, may be regarded as being bathed in lymph. To understand its occurrence in the body one has only to bear in mind its method of origin from the blood. Throughout the entire body there is a rich supply of blood-vessels penetrating every tissue with the exception of the epidermis and some epidermal structures, as the nails and the hair. The plasma of the blood, by the action of physical or chemical processes, the details of which are not yet entirely understood, makes its way through the thin walls of the capillaries, and is thus brought into immediate

<sup>1</sup> *Archiv für Physiologie*, 1899, S. 416.



contact with the tissues, to which it brings the nourishment and oxygen of the blood and from which it removes the waste-products of metabolism. This extravascular lymph is collected into small capillary spaces that in turn open into definite lymphatic vessels. These vessels unite to larger and larger trunks, forming eventually one main trunk, the thoracic or left lymphatic duct, and a second smaller right lymphatic duct, which open into the blood-vessels, each on its own side, at the junction of the subclavian and internal jugular veins. While the supply of lymph in the lymph-vessels may be considered as being derived ultimately entirely from the blood-plasma, it is well to bear in mind that at any given moment this supply may be altered by direct interchange with the plasma on one side and the extravascular lymph permeating the tissue-elements on the other. The intravascular lymph may be augmented, for example, by a flow of water from the plasma into the lymph-spaces, or by a flow from the tissue-elements into the lymph-spaces that surround them. The lymph movement is from the tissues to the veins, and the flow is maintained chiefly by the difference in pressure between the lymph at its origin in the tissues and in the large lymphatic vessels. The continual formation of lymph in the tissues leads to the development of a relatively high pressure in the lymph capillaries, and as a result of this the lymph is forced toward the point of lowest pressure—namely, the points of junction of the large lymph-ducts with the venous system. A fuller discussion of the factors concerned in the movement of lymph will be found in the section on Circulation. As would be inferred from its origin, the composition of lymph is essentially the same as that of blood-plasma. Lymph contains the three blood-proteids, the extractives (urea, fat, lecithin, cholesterolin, sugar), and inorganic salts. The salts are found in the same proportions as in the plasma; the proteids are less in amount, especially the fibrinogen. Lymph coagulates, but does so more slowly and less firmly than the blood. Histologically, lymph consists of a colorless liquid containing a number of leucocytes, and after meals a number of minute fat-droplets; red blood-corpuscles occur only accidentally, and blood-plates, according to most accounts, are likewise normally absent.

**Formation of Lymph.**—The careful researches of Ludwig and his pupils were formerly believed to prove that the lymph is derived directly from the plasma of the blood mainly by filtration through the capillary walls. Emphasis was laid on the undoubted fact that the blood within the capillaries is under a pressure higher than that prevailing in the tissues outside, and it was supposed that this excess of pressure is sufficient to squeeze the plasma of the blood through the very thin capillary walls. Various conditions that alter the pressure of the blood were shown to influence the amount of lymph formed in accordance with the demands of a theory of filtration. Moreover, the composition of lymph as usually given seems to support such a theory, inasmuch as the inorganic salts contained in it are in the same concentration, approximately, as in blood-plasma, while the proteids are in less concentration, following the well-known law that in the filtration of colloids through animal membranes the filtrate is more dilute than the original solution.

blood-plasma also becomes more watery, thus indicating that the increase in water comes from the tissues themselves. Heidenhain designated these bodies as "lymphagogues of the second class." His explanation of their action is that the crystalloid materials introduced into the blood are eliminated by the secretory activity of the endothelial cells, and that they then attract water from the tissue-elements, thus augmenting the flow of lymph. These substances cause but little change in arterial blood-pressure, hence Heidenhain thought that the greater flow of lymph could not be explained by an increased filtration. Starling<sup>1</sup> has shown, however, that, although these bodies may not seriously alter general arterial pressure, they may greatly augment intracapillary pressure, particularly in the abdominal organs. His explanation of the greater flow of lymph in these cases is as follows: "On their injection into the blood the osmotic pressure of the circulating fluid is largely increased. In consequence of this increase water is attracted from lymph and tissues into the blood by a process of osmosis, until the osmotic pressure of the circulating fluid is restored to normal. A condition of hydremic plethora is thereby produced, attended with a rise of pressure in the capillaries generally, especially in those of the abdominal viscera. This rise of pressure will be proportional to the increase in the volume of the blood, and therefore to the osmotic pressure of the solutions injected. The rise of capillary pressure causes great increase in the transudation of fluid from the capillaries, and therefore in the lymph-flow from the thoracic duct." This explanation is well supported by experiments, and seems to obviate the necessity of assuming a secretory action on the part of the capillary walls.

5. One of the most interesting facts developed by the experiments of Heidenhain and his pupils is that after the injection of sugar or neutral salts in the blood the percentage of these substances in the lymph of the thoracic duct may be greater than in the blood itself. It is obviously difficult to explain how this can occur by filtration or diffusion, since it seems to involve the passage of crystalloid bodies from a less concentrated to a more concentrated solution. Cohnstein<sup>2</sup> has endeavored to show a fallacy in these results. He contends that since it requires some time (several minutes) for the lymph to form and pass into the thoracic duct, it is not justifiable to compare the quantitative composition of specimens of blood and lymph taken at the same time. If one compares, in any given experiment, the maximal percentage in the blood of the substance injected with its maximal percentage in the lymph, the latter will be found to be lower. This, however, does not seem to be the case in all the experiments reported. The work of Mendel<sup>3</sup> with sodium iodide seems to establish the fact that when this salt is injected slowly its maximal percentage in the lymph may exceed that in the blood; and in the experiments made by Cohnstein, as well as those by Mendel, it is shown that the percentage of the substance in the lymph remains above that in the blood throughout most of the experiment. In this point, therefore, there seems to be a real difficulty in

<sup>1</sup> *Op. cit.*

<sup>2</sup> *Archiv für die gesammte Physiologie*, 1894-95, Bde. lix., lx. and lxii.

<sup>3</sup> *Journal of Physiology*, 1896, vol. xix, p. 227.



the direct application of the laws of filtration and diffusion to the explanation of the composition of lymph, but it is a point upon which more information is necessary before it alone can be accepted as a basis for a secretion theory. Meanwhile it seems evident that in spite of the very valuable work of Heidenhain, which has added so much to our knowledge of the conditions influencing the formation of lymph, the existence of a definite secretory activity of the endothelial cells of the capillaries has not been proved.

**Summary of the Factors Controlling the Flow of Lymph.**—We may, therefore, adopt, provisionally at least, the so-called mechanical theory of the origin of lymph. Upon this theory the forces in activity are, first, the intra-capillary pressure tending to filter the plasma through the endothelial cells composing the walls of the capillaries; second, the force of diffusion depending upon the inequality in chemical composition of the blood-plasma and the liquid outside the capillaries, or, on the other side, between this liquid and the contents of the tissue-elements; third, the force of osmotic pressure. These three forces acting everywhere control primarily the amount and composition of the lymph, but still another factor must be considered. For when we come to examine the flow of lymph in different parts of the body striking differences are found. It has been shown, for instance, that in the limbs, under normal conditions, the flow is extremely scanty, while from the liver and the intestinal area it is relatively abundant. In fact, the lymph of the thoracic duct may be considered as being derived almost entirely from the latter two regions. Moreover, the lymph from the liver is characterized by a greater percentage of proteids. To account for these differences Starling suggests the plausible explanation of a variation in permeability in the capillary walls. The capillaries seem to have a similar structure all over the body so far as this is revealed to us by the microscope, but the fact that the lymph-flow varies so much in quantity and composition indicates that the similarity is only superficial, and that in different organs the capillary walls may have different internal structures, and therefore different permeabilities. This factor is evidently one of great importance. From the foregoing considerations it is evident that changes in capillary pressure, however produced, may alter the flow of lymph from the blood-vessels to the tissues, by increasing or decreasing, as the case may be, the amount of filtration; changes in the composition of the blood, such as follow periods of digestion, will cause diffusion and osmotic streams tending to equalize the composition of blood and lymph; and changes in the tissues themselves following upon physiological or pathological activity will also disturb the equilibrium of composition, and, therefore, set up diffusion and osmotic currents. In this way a continual interchange is taking place by means of which the nutrition of the tissues is effected, each according to its needs. The details of this interchange must of necessity be very complex when we consider the possibilities of local effects in different parts of the body. The total effects of general changes, such as may be produced experimentally, are simpler, and, as we have seen, are explained satisfactorily by the physical and chemical factors enumerated.



This simple and apparently satisfactory theory has been subjected to critical examination within recent years, and it has been shown that filtration alone does not suffice to explain the composition of the lymph under all circumstances. At present two divergent views are held upon the subject. According to some physiologists, all the facts known with regard to the composition of lymph may be satisfactorily explained if we suppose that this liquid is formed from blood-plasma by the combined action of the physical processes of filtration, diffusion, and osmosis. According to others, it is believed that, in addition to filtration and diffusion, it is necessary to assume an active secretory process on the part of the endothelial cells composing the capillary walls. A discussion upon these points is in progress in current physiological literature, and it is impossible to foresee definitely what the outcome will be, since a final conclusion can be reached only by repeated experimental investigations. The actual condition of our knowledge of the subject can be presented most easily by briefly stating some of the objections that have been raised by Heidenhain<sup>1</sup> to a pure filtration-and-diffusion theory, and indicating how these objections have been met.

1. Heidenhain shows by simple calculations that an impossible formation of lymph would be required, upon the filtration theory, to supply the chemical needs of the organs in various organic and inorganic constituents. Thus, to take an illustration that has been much discussed, one kilogram of cows' milk contains 1.7 grams CaO, and the entire milk of twenty-four hours would contain in round numbers 42.5 grams CaO. Since the lymph contains normally about 0.18 parts of CaO per thousand, it would require 236 liters of lymph per day to supply the necessary CaO to the mammary glands. Heidenhain himself suggests that the difficulty in this case may be met by assuming active diffusion processes in connection with filtration. If, for instance, in the case cited, we suppose that the CaO of the lymph is quickly combined by the tissues of the mammary gland, then the tension of calcium salts in the lymph will be kept at zero, and an active diffusion of calcium into the lymph will occur so long as the gland is secreting. In other words, the gland will receive its calcium by much the same process as it receives its oxygen, and will get its daily supply from a comparatively small bulk of lymph. Strictly speaking, therefore, the difficulty we are dealing with here shows only the insufficiency of a pure filtration theory. It seems possible that filtration and diffusion together would suffice to supply the organs, so far at least as the diffusible substances are concerned.

2. Heidenhain found that occlusion of the inferior vena cava causes not only an increase in the flow of lymph—as might be expected, on the filtration theory, from the consequent rise of pressure in the capillary regions—but also an increased concentration in the percentage of proteid in the lymph. This latter fact has been satisfactorily explained by the experiments of Starling.<sup>2</sup> According to this observer, the lymph formed in the liver is normally more

<sup>1</sup> *Archiv für die gesammte Physiologie*, 1891, Bd. xlix. S. 209.

<sup>2</sup> *Journal of Physiology*, 1894, vol. xvi. p. 234.

concentrated than that of the rest of the body. The occlusion of the vena cava causes a marked rise in the capillary pressure in the liver, and most of the increased lymph-flow under these circumstances comes from the liver, hence the greater concentration. The results of this experiment, therefore, do not antagonize the filtration-and-diffusion theory.

3. Heidenhain discovered that extracts of various substances which he designated as "lymphagogues of the first class" cause a marked increase in the flow of lymph from the thoracic duct, the lymph being more concentrated than normal, and the increased flow continuing for a long period. Nevertheless, these substances cause little, if any, increase in general arterial pressure; in fact, if injected in sufficient quantity they produce usually a fall of arterial pressure. The substances belonging to this class comprise such things as peptone, egg-albumin, extracts of liver and intestine, and especially extracts of the muscles of crabs, crayfish, mussels, and leeches. Heidenhain supposed that these extracts contain an organic substance which acts as a specific stimulus to the endothelial cells of the capillaries and increases their secretory action. The results of the action of these substances has been differently explained by those who are unwilling to believe in the secretion theory. Starling<sup>1</sup> finds experimentally that the increased flow of lymph in this case, as after obstruction of the vena cava, comes mainly from the liver. There is at the same time in the portal area an increased pressure that may account in part for the greater flow of lymph; but, since this effect upon the portal pressure lasts but a short time, while the greater flow of lymph may continue for one or two hours, it is obvious that this factor alone does not suffice to explain the result of the injections. Starling suggests, therefore, that these extracts act pathologically upon the blood-capillaries, particularly those of the liver, and render them more permeable, so that a greater quantity of concentrated lymph filters through them. Starling's explanation is supported by the experiments of Popoff.<sup>2</sup> According to this observer, if the lymph is collected simultaneously from the lower portion of the thoracic duct, which conveys the lymph from the abdominal organs, and from the upper part, which contains the lymph from the head, neck, etc., it will be found that injection of peptone increases the flow from only the abdominal organs. Popoff finds also that the peptone causes a dilatation in the intestinal circulation and a marked rise in the portal pressure. At the same time there is some evidence of injury to the walls of the blood-vessels from the occurrence of extravasations in the intestine. As far, therefore, as the action of the lymphagogues of the first class is concerned, it may be said that the advocates of the filtration-and-diffusion theory have suggested a plausible explanation in accord with their theory. The facts emphasized by Heidenhain with regard to this class of substances do not compel us to assume a secretory function for the endothelial cells.

4. Injection of certain crystalline substances, such as sugar, NaCl, and other neutral salts, causes a marked increase in the flow of lymph from the thoracic duct. The lymph in these cases is more dilute than normal, and the

<sup>1</sup> *Journal of Physiology*, 1894, vol. xvii. p. 30. <sup>2</sup> *Centralblatt für Physiologie*, 1895, Bd. ix. No. 2.



blood-plasma also becomes more watery, thus indicating that the increase in water comes from the tissues themselves. Heidenhain designated these bodies as "lymphagogues of the second class." His explanation of their action is that the crystalloid materials introduced into the blood are eliminated by the secretory activity of the endothelial cells, and that they then attract water from the tissue-elements, thus augmenting the flow of lymph. These substances cause but little change in arterial blood-pressure, hence Heidenhain thought that the greater flow of lymph could not be explained by an increased filtration. Starling<sup>1</sup> has shown, however, that, although these bodies may not seriously alter general arterial pressure, they may greatly augment intracapillary pressure, particularly in the abdominal organs. His explanation of the greater flow of lymph in these cases is as follows: "On their injection into the blood the osmotic pressure of the circulating fluid is largely increased. In consequence of this increase water is attracted from lymph and tissues into the blood by a process of osmosis, until the osmotic pressure of the circulating fluid is restored to normal. A condition of hydremic plethora is thereby produced, attended with a rise of pressure in the capillaries generally, especially in those of the abdominal viscera. This rise of pressure will be proportional to the increase in the volume of the blood, and therefore to the osmotic pressure of the solutions injected. The rise of capillary pressure causes great increase in the transudation of fluid from the capillaries, and therefore in the lymph-flow from the thoracic duct." This explanation is well supported by experiments, and seems to obviate the necessity of assuming a secretory action on the part of the capillary walls.

5. One of the most interesting facts developed by the experiments of Heidenhain and his pupils is that after the injection of sugar or neutral salts in the blood the percentage of these substances in the lymph of the thoracic duct may be greater than in the blood itself. It is obviously difficult to explain how this can occur by filtration or diffusion, since it seems to involve the passage of crystalloid bodies from a less concentrated to a more concentrated solution. Cohnstein<sup>2</sup> has endeavored to show a fallacy in these results. He contends that since it requires some time (several minutes) for the lymph to form and pass into the thoracic duct, it is not justifiable to compare the quantitative composition of specimens of blood and lymph taken at the same time. If one compares, in any given experiment, the maximal percentage in the blood of the substance injected with its maximal percentage in the lymph, the latter will be found to be lower. This, however, does not seem to be the case in all the experiments reported. The work of Mendel<sup>3</sup> with sodium iodide seems to establish the fact that when this salt is injected slowly its maximal percentage in the lymph may exceed that in the blood; and in the experiments made by Cohnstein, as well as those by Mendel, it is shown that the percentage of the substance in the lymph remains above that in the blood throughout most of the experiment. In this point, therefore, there seems to be a real difficulty in

<sup>1</sup> *Op. cit.*

<sup>2</sup> *Archiv für die gesammte Physiologie*, 1894-95, Bde. liz., lx. and lxii.

<sup>3</sup> *Journal of Physiology*, 1896, vol. xix. p. 227



the direct application of the laws of filtration and diffusion to the explanation of the composition of lymph, but it is a point upon which more information is necessary before it alone can be accepted as a basis for a secretion theory. Meanwhile it seems evident that in spite of the very valuable work of Heidenhain, which has added so much to our knowledge of the conditions influencing the formation of lymph, the existence of a definite secretory activity of the endothelial cells of the capillaries has not been proved.

**Summary of the Factors Controlling the Flow of Lymph.**—We may, therefore, adopt, provisionally at least, the so-called mechanical theory of the origin of lymph. Upon this theory the forces in activity are, first, the intra-capillary pressure tending to filter the plasma through the endothelial cells composing the walls of the capillaries; second, the force of diffusion depending upon the inequality in chemical composition of the blood-plasma and the liquid outside the capillaries, or, on the other side, between this liquid and the contents of the tissue-elements; third, the force of osmotic pressure. These three forces acting everywhere control primarily the amount and composition of the lymph, but still another factor must be considered. For when we come to examine the flow of lymph in different parts of the body striking differences are found. It has been shown, for instance, that in the limbs, under normal conditions, the flow is extremely scanty, while from the liver and the intestinal area it is relatively abundant. In fact, the lymph of the thoracic duct may be considered as being derived almost entirely from the latter two regions. Moreover, the lymph from the liver is characterized by a greater percentage of proteids. To account for these differences Starling suggests the plausible explanation of a variation in permeability in the capillary walls. The capillaries seem to have a similar structure all over the body so far as this is revealed to us by the microscope, but the fact that the lymph-flow varies so much in quantity and composition indicates that the similarity is only superficial, and that in different organs the capillary walls may have different internal structures, and therefore different permeabilities. This factor is evidently one of great importance. From the foregoing considerations it is evident that changes in capillary pressure, however produced, may alter the flow of lymph from the blood-vessels to the tissues, by increasing or decreasing, as the case may be, the amount of filtration; changes in the composition of the blood, such as follow periods of digestion, will cause diffusion and osmotic streams tending to equalize the composition of blood and lymph; and changes in the tissues themselves following upon physiological or pathological activity will also disturb the equilibrium of composition, and, therefore, set up diffusion and osmotic currents. In this way a continual interchange is taking place by means of which the nutrition of the tissues is effected, each according to its needs. The details of this interchange must of necessity be very complex when we consider the possibilities of local effects in different parts of the body. The total effects of general changes, such as may be produced experimentally, are simpler, and, as we have seen, are explained satisfactorily by the physical and chemical factors enumerated.

### III. CIRCULATION.

#### PART I.—THE MECHANICS OF THE CIRCULATION OF THE BLOOD AND OF THE MOVEMENT OF THE LYMPH.

##### A. GENERAL CONSIDERATIONS.

THE metaphorical phrase "circulation of the blood" means that every particle of blood, so long as it remains within the vessels, moves along a path which, no matter how tortuous, finally returns into itself; that, therefore, the particles which pass a given point of that path may be the same which have passed it many times already; and that the blood moves in its path always in a definite direction, and never in the reverse.

The discoverer of these weighty facts was "William Harvey, physician, of London," as he styled himself. In the lecture notes of the year 1616, mostly in Latin, which contain the earliest record of his discovery, he declares that a "perpetual movement of the blood in a circle is caused by the beat of the heart" ("perpetuum sanguinis motum in circulo fieri pulsu cordis").<sup>1</sup> For a long time afterward the name of the discoverer was coupled with the expression which he himself had introduced, and the true movement of the blood was known as the "Harveian circulation."<sup>2</sup>

**Course of the Blood.**—The metaphorical circle of the blood-path may be shown by such a diagram as Figure 8.

If, in the body of a warm-blooded animal, we trace the course of a given particle, beginning at the point where it leaves the right ventricle of the heart, we find that course to be as follows: From the trunk of the pulmonary artery (*PA*) through a succession of arterial branches derived therefrom into a capillary of the lungs (*PC*); out of that, through a succession of pulmonary veins, to one of the main pulmonary veins (*PI*) and the left auricle of the heart (*LA*); thence to the left ventricle (*LV*); to the trunk of the aorta (*A*); through a succession of arterial branches derived therefrom into any capillary (*C*) not supplied by the pulmonary artery; out of that, through a succession of veins (*V*) to one of the venæ cavæ or to a vein of the heart itself; thence to the right auricle (*RA*), to the right ventricle (*RV*), and to the trunk of the pulmonary artery, where the tracing of the circuit began.

<sup>1</sup> William Harvey: *Prelectiones Anatomiae Universalis*, edited, with an autotype reproduction of the original, by a committee of the Royal College of Physicians of London, 1886, p. 80.

<sup>2</sup> Harvey's discovery of the circulation was first published in the modern sense in his work *Exercitatio anatomica de motu cordis et sanguinis in animalibus*, Francofurti, 1628. This great classic can be read in English in the following: *On the Motion of the Heart and Blood in Animals*. By William Harvey, M. D.; Willis's translation, revised and edited by Alex. Bowie, 1889.



It must be noted here that a particle of blood which traverses a capillary of the spleen, of the pancreas, of the stomach, or of the intestines, and enters the portal vein, must next traverse a series of venous branches of diminishing size, and a capillary of the liver, before entering the succession of veins which will conduct the particle to the ascending vena cava (compare Figs. 8 and 9).

Most of the blood, therefore, which leaves the liver has traversed two sets of capillaries, connected with one another by the portal vein, since quitting the arterial system. This ar-

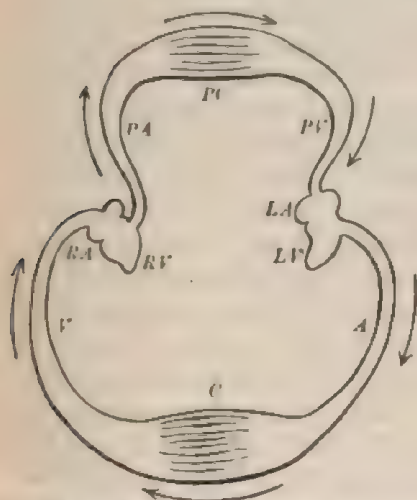


FIG. 8.—General diagram of the circulation: the arrows indicate the course of the blood: *PA*, pulmonary artery; *PC*, pulmonary capillaries; *PV*, pulmonary veins; *LA*, left auricle; *LV*, left ventricle; *A*, systemic arteries; *C*, systemic capillaries; *V*, systemic veins; *RA*, right auricle; *RV*, right ventricle.

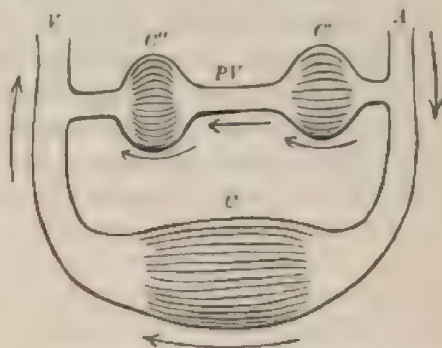


FIG. 9.—Diagram of the portal system: the arrows indicate the course of the blood: *A*, arterial system; *V*, venous system; *C'*, capillaries of the spleen, pancreas, and alimentary canal; *PV*, portal vein; *C''*, capillaries of the liver; *C*, the rest of the systemic capillaries. The hepatic artery is not represented.

range is of extreme importance for the physiology of nutrition. An arrangement of the same order, though less conspicuous, exists in the kidney.

**Causes of the Blood-flow.**—The force by which the blood is driven from the right to the left side of the heart through the capillaries which are related to the respiratory surface of the lungs, is nearly all derived from the contraction of the muscular wall of the right ventricle, which narrows the cavity thereof and ejects the blood contained in it; the force by which the blood is driven from the left to the right side of the heart through all the other capillaries of the body, often called the "systemic" capillaries, is derived nearly all from the contraction of the muscular wall of the left ventricle, which narrows its cavity and ejects its contents. The contractions of the two ventricles are simultaneous. The force derived from each contraction is generated by the conversion of potential energy, present in the chemical constituents of the muscular tissue, into energy of visible motion; a part also of the potential energy at the same time becoming manifest as heat. In the maintenance of the circulation the force generated by the heart is to a very subordinate degree supplemented by the forces which produce the aspiration of the chest and by



the force generated by the contractions of the skeletal muscles throughout the body (see p. 95).

**Mode of Working of the Pumping Mechanism.**—During each contraction or "systole" of the ventricles the blood is ejected into the arteries only, because at that time the auriculo-ventricular openings are each closed by a valve. During the immediately succeeding "diastole" of the ventricles, which consists in the relaxation of their muscular walls and the dilatation of their cavities, blood enters the ventricles by way of the auricles only, because at that time the arterial openings are closed each by a valve which was open during the ventricular systole; and because the auriculo-ventricular valves which were closed during the systole of the ventricles are open during their diastole. During the first and longer part of the diastole of the ventricles the auricles, too, are in diastole; the whole heart is in repose; and blood is not only entering the auricles, but passing directly through them into the ventricles. Near the end of the ventricular diastole a brief simultaneous systole of both auricles takes place, during which they, too, narrow their cavities by the muscular contraction of their walls, and eject into the ventricles blood which had entered the auricles from the "systemic" and pulmonary veins respectively. The systole of the auricles ends immediately before that of the ventricles begins. The brief systole of the auricles is succeeded by their long diastole, which corresponds in time with the whole of the ventricular systole and with the greater part of the succeeding ventricular diastole. During the diastole of the auricles blood is entering them out of the veins. Thus it is seen that the direction in which the blood is forced is essentially determined by the mechanism of the valves at the apertures of the ventricles; and that it is due to these valves that the blood moves only in the definite direction before alluded to. In the words, again, of Harvey's note-book, at this point written in English, the blood is perpetually transferred through the lungs into the aorta "as by two clacks of a water bellows to rayse water."<sup>1</sup>

**Pulmonary Blood-path.**—In the birds and mammals the entire breadth of the blood-path, at one part of the physiological circle, consists in the capillaries spread out beneath the respiratory surface of the lungs. The right side of the heart exists only to force the blood into and past this portion of its circuit, where, as in the systemic capillaries, the friction due to the fineness of the tubes causes much resistance to the flow. This great comparative development of the pulmonary portion of the blood-path in the warm-blooded vertebrates is related to the activity, in them, of the respiration of the tissues, which calls for a corresponding activity of function at the respiratory surface of the lungs, and for a rapid renewal in every systemic capillary of the internal respiratory medium, the blood. This rapid renewal implies a rapid circulation; and that the speed is great with which the circuit of the heart and vessels is completed has been proven by experiment, the method being too complicated for description here.<sup>2</sup>

<sup>1</sup> *Prelectiones*, etc., p. 80.

<sup>2</sup> Karl Vierordt: *Die Erscheinungen und Gesetze der Stromgeschwindigkeiten des Blutes*. 2te Ausgabe, 1882.

**Rapidity of the Circulation.**—By experiment the shortest time has been measured which is taken by a particle of blood in passing from a point in the external jugular vein of a dog to and through the right cavities of the heart, the pulmonary vessels, the left cavities of the heart, the commencement of the aorta, and the arteries, capillaries, and veins of the head, to the starting-point, or to the same point of the vein of the other side. This time has been found to be from fifteen to eighteen seconds. Naturally, the time would be different in different kinds of animals and in the different circuits in the same individual.

**Order of Study of the Mechanics of the Circulation.**—The significance and the fundamental facts of the circulation have now been indicated. Its phenomena must next be studied in detail.<sup>1</sup> As the blood moves in a circle, we may, in order to study the movement, strike into the circle at any point. It will, however be found both logical and instructive to study first the movement of the blood in the capillaries, whether systemic or pulmonary. It is only in passing through these and the minute arteries and veins adjoining that the blood fulfils its essential functions; elsewhere it is in transit merely. Moreover, it is only in the minute vessels that the blood and the nature of its movement are actually visible.

After the capillary flow shall have become familiar, it will be found that the other phenomena of the circulation will fall naturally into place as indicating how that flow is caused, is varied, and is regulated.

#### B. THE MOVEMENT OF THE BLOOD IN THE CAPILLARIES AND IN THE MINUTE ARTERIES AND VEINS.

**Characters of the Capillaries.**—Each of the vessels which compose the immensely multiplied capillary network of the body is a tube, commonly of less than one millimeter in length, and of a few one-thousandths only of a millimeter in calibre, the wall of which is so thin as to elude accurate measure-



FIG. 10.—A capillary from the mesentery of the frog (Ranvier).

ment. The calibre of each capillary may vary from time to time. These facts indicate the minute subdivision of the blood-stream in the lungs, and among the tissues—that is, at the two points of its course where the essential functions of the blood are fulfilled. These facts also show the shortness of

<sup>1</sup> The following is a very valuable book of reference: Robert Tigerstedt: *Lehrbuch der Physiologie des Kreislaufes*, 1893.



the distance to be traversed by the blood while fulfilling these functions; and explain the importance of the comparatively slow rate at which it will be found to move through that short distance. The histological study of a typical capillary (see Fig. 10) shows that its thin wall is composed of a single layer only of living flat endothelial cells set edge to edge in close contact; and that the edges of the cells are united by a small quantity of the so-called cement-substance. If the capillary be traced in either anatomical direction, the wall of the vessel is seen to become less thin and more complex, till it merges into that of a typical arteriole or venule, the walls of which are still delicate, though less so than that of a capillary. That the capillary walls are so thin and soft, and are made of living cells, are very important facts as regards the relations between blood and tissue. It is of great importance for the variation of the blood-supply to a part that they are also distensible, elastic, and possibly contractile.

**Direct Observation of the Flow in the Small Vessels.**—The capillary flow is visible under the compound microscope, best by transmitted light, in the transparent parts of both warm-blooded and cold-blooded animals. It is important that the phenomena observed in the latter should be compared with observations upon the higher animals; but the fundamental facts can be most fruitfully studied in the frog, tadpole, or fish, inasmuch as no special arrangements are needed to maintain the temperature of the exposed parts of these animals. Moreover, their large oval and nucleated red blood-corpuscles are well fitted to indicate the forces to which they are subjected. The capillary movement, therefore, will be described as seen in the frog; it being understood that the phenomena are similar in the other vertebrates. In the frog the movement may be studied in the lung, the mesentery, the urinary bladder, the tongue, or the web between the toes. During such study the proper wall of the living capillary is hardly to be seen, but only the line on each side which marks the profile of its cavity. Even the proper walls of the transparent arterioles and venules are but vaguely indicated. The plasma of the blood, too, has so nearly the same index of refraction as the tissues, that it remains invisible. It is only the red corpuscles and leucocytes that are conspicuous; and when one speaks of seeing the blood in motion, he means, strictly speaking, that he sees the moving corpuscles, and can make out the calibre of the vessels in which they move. The observer uses as low a power of the microscope as will suffice, and takes first a general survey of the minute arteries, veins, and capillaries of the part he is studying, noting their form, size, and connections. In the arteries and veins he sees that the size of the vessels is ample in comparison with that of the corpuscles; that, in the veins, the movement of the blood is steady, but in the arteries accelerated and retarded, with a rhythm corresponding to that of the heart's beat. In some parts, if the circumstances of the observation have somewhat retarded the circulation, the individual red corpuscles can be distinguished in the veins, while in the arteries they cannot, as at all times they shoot past the eye too swiftly. The fundamental observation now is verified that the blood is incessantly moving out of the arteries, through the capillaries, into the veins.



**Behavior of the Red Corpuscles.**—Capillaries will readily be found in which the red corpuscles move two or three abreast, or only in single file. They generally go with their long diameters parallel to, or moderately oblique to, the current. In no case will any blockade of corpuscles occur, so long as the parts are normal. The numerous red corpuscles are seen to be well fitted by their softness and elasticity, as well as by their form and size, for moving through the narrow channels. They bend easily upon themselves as they turn sharp corners, but instantly regain their form when free to do so (see Fig. 11). A very common occurrence is for a corpuscle to catch upon the edge which parts two capillaries at a bifurcation of the network. For some time the corpuscle may remain doubled over the projection like a sack thrown across a horse's back; but, after oscillating for a while, it will be disengaged, at once return to its own shape, and disappear in one of the two branches

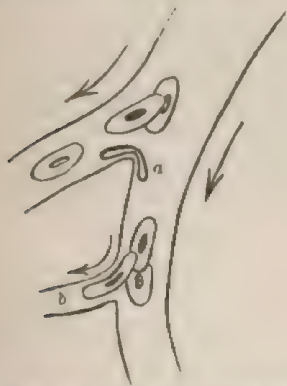


FIG. 11.—To illustrate the behavior of red corpuscles in the capillaries: the arrows mark the course of the blood: *a*, a "saddle-bag" corpuscle; *b*, a corpuscle bending upon itself as it enters a side branch.

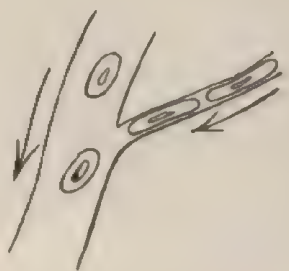


FIG. 12.—To illustrate the deformity produced in red corpuscles in passing through a capillary of a less diameter than themselves.

(see Fig. 11). It is instructive to watch red corpuscles passing in single file through a capillary the calibre of which, at the time, is actually less than the shorter diameter of the corpuscles. Through such a capillary each corpuscle is squeezed, with lengthening and narrowing of its soft mass, but on emerging into a larger vessel its elasticity at once corrects even this deformity; it regains its form, and passes on (Fig. 12).

**Evidences of Friction.**—In the minute vessels, capillary and other, certain appearances should carefully be observed which are the direct ocular evidence of that friction which we shall find to be one of the prime forces concerned in the blood-movement, to which it constitutes a strong resistance. If, in a channel which admits three red corpuscles beside one another, three be observed when just abreast, it will be found that very soon the middle one forges ahead, indicating that the stream is swiftest at its core. This is because the friction within the vessel is least in the middle, and progressively greater outward to the wall (Fig. 13). In the small veins the signs of friction are

strikingly seen, as the outer layers among the numerous corpuscles lag conspicuously. In the arterioles similar phenomena are seen if the normal swiftness of movement become sufficiently retarded for the individual corpuscles to be visible.

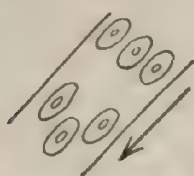


FIG. 13.—To illustrate the forging ahead of a corpuscle at the centre of the blood-stream. The arrow marks the direction of the blood.



FIG. 14.—The inert layer of plasma in the small vessels.

An appearance which also tells of friction is that of the so-called "inert layer" of plasma.<sup>1</sup> In vessels, of whatever kind, which are wide enough for several corpuscles to pass abreast, it is seen that all the red corpuscles are always separated from the profile of their channel by a narrow clear and colorless interval—occupied, of course, by plasma. This is caused by the excess of the friction in the layers nearest to the vascular wall (see Fig. 14). The friction thus indicated, other things being equal, is less in a dilated than in a contracted tube; and less in a sluggish than in a rapid stream. It probably varies also with changes of an unknown kind in the condition of the cells of the vascular wall.

**Behavior of the Leucocytes.**—If the behavior of the leucocytes be watched, it will be seen to differ markedly from that of the red corpuscles, at least when the blood-stream is somewhat retarded, as it so commonly is under the microscope. Whereas the friction within the vessels causes the throng of red corpuscles to occupy the core of the stream, the scantier leucocytes may move mainly in contact with the wall, and thus be present freely in the inert layer of plasma. Naturally their progression is then much slower and more irregular than that of the red disks. Indeed, the leucocytes often adhere to the wall for a while, in spite of shocks from the red cells which pass them. Moreover, the spheroidal leucocyte rolls over and over as it moves along the wall in a way very different from the progression of the red disk, which only occasionally may revolve about one of its diameters. A leucocyte entangled among the red cells near the middle of the stream is seen generally not only to move onward but also to move outward toward the wall, and, before long, to join the other leucocytes which are bathed by the inert layer of plasma. It is due solely to the lighter specific gravity of the leucocytes that, under the forces at work within the smaller vessels, they go to the wall, while the denser disks go to the core of the current. This has been proved experimentally by driving through artificial capillaries a fluid having in suspension particles of two kinds. Those of the lighter kind go to the wall, of the heavier

<sup>1</sup> Poiseuille: "Recherches sur les causes du mouvement du sang dans les vaisseaux capillaires," *Académie des Sciences—Savants étrangers*, 1835.



kind to the core, even when the nature and form of the particles employed are varied.<sup>1</sup>

**Emigration of Leucocytes.**—It has been said that a leucocyte may often adhere for a time to the wall of the capillary, or of the arteriole or venule, in which it is. Sometimes the leucocyte not only adheres to the wall, but passes through it into the tissue without by a process which has received the name of "emigration."<sup>2</sup> A minute projection from the protoplasm of the leucocyte is thrust into the wall, usually where this consists of the soft cement-substance between the endothelial cells. The delicate pseudopod is seen presently to have pierced the wall, to have grown at the expense of the main body of the cell, and to have become knobbed at the free end which is in the tissue. Later, the flowing of the protoplasm will have caused the leucocyte to assume something of a dumb-bell form, with one end within the blood-vessel and the other without. Then, by converse changes, the flowing protoplasm comes to lie mainly within the lymph-space, with a small knob only within the vessel; and, lastly, this knob too flows out; what had been the neck of the dumb-bell shrinks and is withdrawn into the cell-body, and the leucocyte now lies wholly without the blood-vessel, while the minute breach in the soft wall has closed behind the retiring pseudopod. This phenomenon has been seen in capillaries, venules, and arterioles, but mainly in the two former. It seems to be due to the amoeboid properties of the leucocytes as well as to purely physical causes. Emigration, although it may probably occur in normal vessels, is strikingly seen in inflammation, in which there seems to be an increased adhesiveness between the vascular wall and the various corpuscles of the blood.

**Speed of the Blood in the Minute Vessels.**—As a measure of the speed of the blood in a vessel, we may fairly take the speed of the red corpuscles. It must, however, be remembered that as the friction increases toward the wall, the speed of the red corpuscles is least in the outer layers of blood, and increases rapidly toward the long axis of the tube. At the core of the stream the speed may be twice as great as near the wall. As we have seen, the stream of red corpuscles in an arteriole is rapid and pulsating. In the corresponding venule, which is commonly a wider vessel, the stream is less swift, and its pulse has disappeared. In the capillary network between the two vessels the speed of the red corpuscles is evidently slower than in either arteriole or venule; and here, as in the veins, no pulse is to be seen; the pulse comes to an end with the artery which exhibits it. In one capillary of the network under observation the movement may be more active than in another; and even in a given capillary irregular variations of speed at different moments may be observed. Where two capillaries in which the pressure is nearly the same are connected by a cross-branch, the red corpuscles in this last may sometimes even be seen to

<sup>1</sup> A. Schklarewsky: "Ueber das Blut und die Suspensionsflüssigkeiten," *Pflüger's Archiv für die gesammte Physiologie*, 1868, Bd. i. S. 603.

<sup>2</sup> For the literature of emigration see B. Thoma: *Text-book of General Pathology and Pathological Anatomy*, translated by A. Bruce, 1890, vol. i. p. 344.



oscillate, come to a standstill, and then reverse the direction of their movement, and return to the capillary whence they had started. Naturally, no such reversal will ever be seen in a capillary which springs directly from an artery or which directly joins a vein. It will be remembered, however, that any apparent speed of a corpuscle is much magnified by the microscope, and that therefore the variations referred to are comparatively unimportant. We may, in fact, without material error, treat the speed of the blood in the capillaries which intervene between the arteries and veins of a region as approximately uniform for an ordinary period of observation, as the minute variations will tend to compensate for one another. This speed is sluggish, as already noted. In the capillaries of the web of the frog's foot it has been found to be about 0.5 millimeter per second. The causes of this sluggishness will be set forth later. That the very short distance between artery and vein is traversed slowly, deserves to be insisted on, as thus time is afforded for the uses of the blood to be fulfilled.

**Capillary Blood-pressure.**—The pressure of the blood against the capillary wall is low, though higher than that of the lymph without. This pressure is subject to changes, and is readily yielded to by the elastic and delicate wall. From these changes of pressure changes of calibre result. The microscope tells us less about the capillary blood-pressure than about the other phenomena of the flow; but the microscope may sometimes show one striking fact. In a capillary district under observation, a capillary not noted before may suddenly start into view as if newly formed under the eye. This is because its calibre has been too small for red corpuscles and leucocytes to enter, until some slight increase of pressure has dilated the transparent tube, hitherto filled with transparent plasma only. This dilatation has admitted corpuscles, and has caused the vessel to appear.

That the capillary pressure is low is shown, moreover, by the fact that when one's finger is pricked or slightly cut, the blood simply drips away; that it does not spring in a jet, as when an artery of any size has been divided. That the capillary pressure is low may also be shown, and more accurately, by the careful scientific application of a familiar fact: If one press with a blunt lead-pencil upon the skin between the base of a finger-nail and the neighboring joint, the ruddy surface becomes pale, because the blood is expelled from the capillaries and they are flattened. If delicate weights be used, instead of the pencil, the force can be measured which just suffices to whiten the surface somewhat, that is, to counterbalance the pressure of the distending blood, which pressure thus can be measured approximately. It has been found to be very much lower than the pressure in the large arteries, considerably higher than that in the large veins, and thus intermediate between the two; whereas the blood-speed in the capillaries is less than the speed in either the arteries or the veins. The pressure in the capillaries, measured by the method just described, has been found to be equal to that required to sustain against gravity a column of mercury from 24 to 54 milli-

meters high ; or, in the parlance of the laboratory, has been found equal to from 24 to 54 millimeters of mercury.<sup>1</sup>

**Summary of the Capillary Flow.**—Whether in the lungs or in the rest of the body, the general characters of the capillary flow, as learned from direct inspection and from experiment, may be summed up as follows : The blood moves through the capillaries toward the veins with much friction, continuously, slowly, without pulse, and under low pressure. To account for these facts is to deal systematically with the mechanics of the circulation ; and to that task we must now address ourselves.

### C. THE PRESSURE OF THE BLOOD IN THE ARTERIES, CAPILLARIES, AND VEINS.

Why does the blood move continuously out of the arteries through the capillaries into the veins ? Because there is continuously a high pressure of blood in the arteries and a low pressure in the veins, and from the seat of high to that of low pressure the blood must continuously flow through the capillaries, where pressure is intermediate, as already stated.

**Method of Studying Arterial and Venous Pressure, and General Results.**—Before stating quantitatively the differences of pressure, we must see how they are ascertained for the arteries and veins. The method of obtaining the capillary pressure has been referred to already. If, in the neck of a mammal, the left common carotid artery be clamped in two places, it can, without loss of blood, be divided between the clamps, and a long straight glass tube, open at both ends, and of small calibre, can be tied into that stump of the artery which is still connected with the aorta, and which is called the "proximal" stump. If now the glass tube be held upright, and the clamp be taken off which has hitherto closed the artery between the tube and the aorta, the blood will mount in the tube, which is open at the top, to a considerable height, and will remain there. The external jugular vein of the other side should have been treated in the same way, but its tube should have been inserted into the "distal" stump—that is, the stump connected with the veins of the head, and not with the subclavian veins. If the clamp between the tube and the head have been removed at nearly the same time with that upon the artery, the blood may have mounted in the upright venous tube also, but only to a small distance. To cite an actual case in illustration, in a small etherized dog the arterial blood-column has been seen to stand at a height of about 155 centimeters above the level of the aorta, the height of the venous column about 18 centimeters above the same level. The heights of the arterial and venous columns of blood measure the pressures obtaining within the aorta and the veins of the head respectively, while at the same time the circulation continues to be free through both the aorta and the venous network. Therefore, in the dog above referred to, the aortic pressure was between eight and nine

<sup>1</sup> N. v. Kries: "Ueber den Druck in den Blutcapillaren der menschlichen Haut," *Berichte über die Verhandlungen der k. sächsischen Gesellschaft der Wissenschaften zu Leipzig, math.-physische Classe*, 1875, S. 149.



times as great as that in the smaller veins of the head. As, during such an experiment, the blood is free to pass from the aorta through one carotid and both vertebral arteries to the head, and to return through all the veins of that part, except one external jugular, to the vena cava, it is demonstrated that there must be a continuous flow from the aorta, through the capillaries of the head, into the veins, because the pressure in the aorta is many times as great as the pressure in the veins. Obviously, such an experiment, although very instructive, gives only roughly qualitative results.

Two things will be noted, moreover, in such an experiment. One is that the venous column is steady; the other is that the arterial column is perpetually fluctuating in a rhythmic manner. The top of the arterial column shows a regular rise and fall of perhaps a few centimeters, the rhythm of which is the same as that of the breathing of the animal; and, while the surface is thus rising and falling, it is also the seat of frequent flickering fluctuations of smaller extent, the rhythm of which is regular, and agrees with that of the heart's beat. At no time, however, do the respiratory fluctuations of the arterial column amount to more than a fraction of its mean height; compared to which last, again, the cardiac fluctuations are still smaller. It is clear, then, that the aortic pressure changes with the movements of the chest, and with the systoles and diastoles of the left ventricle. But stress is laid at present upon the fact that the aortic pressure at its lowest is several times as high as the pressure in the smaller veins of the head. Therefore, the occurrence of incessant fluctuations in the aortic pressure cannot prevent the continuous movement of the blood out of the arteries, through the capillaries, into the veins.

The upright tubes employed in the foregoing experiment are called "manometers."<sup>1</sup> They were first applied to the measurement of the arterial and venous blood-pressures by a clergyman of the Church of England, Stephen Hales, rector of Farringdon in Hampshire, who experimented with them upon the horse first, and afterward upon other mammals. He published his method and results in 1733.<sup>2</sup> The height of the manometric column is a true measure of the pressure which sustains it; for the force derived from gravity with which the blood in the tube presses downward at its lower opening is exactly equal to the force with which the blood in the artery or vein is pressed upward at the same opening. The downward force exerted by the column of blood varies directly with the height of the column, but, by the laws of fluid pressure, does not vary with the calibre of the manometer, which calibre may therefore be settled on other grounds. It follows also that the arterial and venous manometers need not be of the same calibre. Were, however, another fluid than the blood itself used in the manometer to measure a given intravascular pressure, as is easily possible, the height of the column would differ from that of the column of blood. For a given pressure the height

<sup>1</sup> From *μανός*, rare. The name was given from such tubes being used to measure the tension of gases.

<sup>2</sup> Stephen Hales: *Statical Essays: containing Hemostaticks*, etc., London, 1733, vol. ii. p. 1.



of the column is inverse to the density of the manometric fluid. For example, a given pressure will sustain a far taller column of blood than of mercury.

**The Mercurial Manometer.**—The method of Hales, in its original simplicity, is valuable from that very simplicity for demonstration, but not for research. The clotting of the blood soon ends the experiment, and, while it continues, the tallness of the tube required for the artery, and the height of the column of blood, are very inconvenient. It is essential to understand next the principles of the more exact instruments employed in the modern laboratory.

In 1828 the French physician and physiologist J. L. M. Poiseuille devised means both of keeping the blood from clotting in the tubes, and of using as a measuring fluid the heavy mercury instead of the much lighter blood. He thereby secured a long observation, a low column, and a manageable manometer.<sup>1</sup> The "mercurial manometer" of to-day is that of Poiseuille, though modified (see Fig. 15). In an improved form it consists of a glass tube open at both ends, and bent upon itself to the shape of the letter U. This is held upright by an iron frame. If mercury be poured into one branch of the U, it will fill both branches to an equal height. If fluid be driven down upon the mercury in one branch or "limb" of the tube, it will drive some of the mercury out of that limb into the other, and the two surfaces of the mercury may come to rest at very unequal levels. The difference of level, expressed in millimeters,

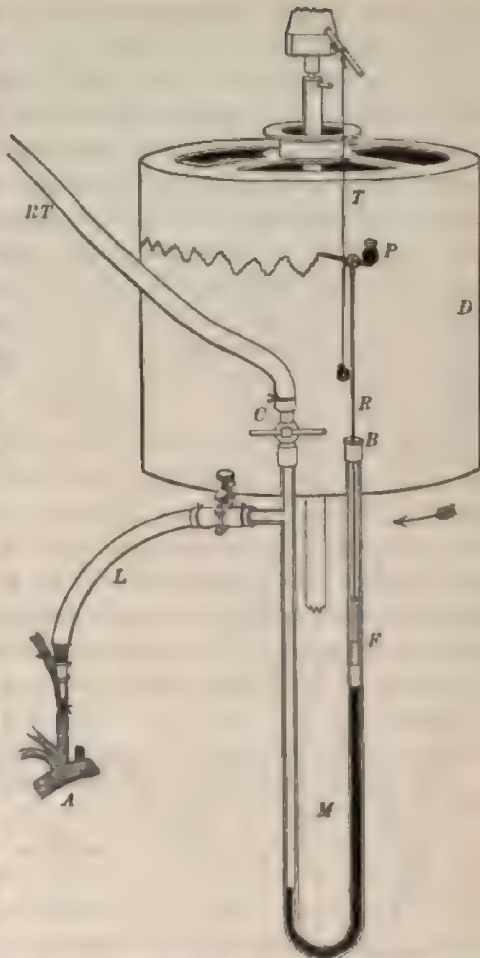


FIG. 15.—Diagram of the recording mercurial manometer and the kymograph, the mercury is indicated in deep black: *M*, the manometer, connected by the leaden pipe, *L*, with a glass cannula tied into the proximal stump of the left common carotid artery of a dog: *A*, the aorta; *C*, the stopcock, by opening which the manometer may be made to communicate through *RT* the rubber tube, with a pressure-bottle of solution of sodium carbonate; *F*, the float of ivory and hard rubber; *R*, the light steel rod, kept perpendicular by *B*, the steel bearing; *P*, the glass capillary pen charged with quickly drying ink; *T*, a thread which is caused, by the weight of a light ring of metal suspended from it, to press the pen obliquely and gently against the paper with which is covered *D*, the brass "drum" of the kymograph, which drum revolves in the direction of the arrow. The supports of the manometer and the body and clock-work of the kymograph are omitted for the sake of simplicity. The aorta and its branches are drawn disproportionately large for the sake of clearness.

<sup>1</sup> J. L. M. Poiseuille: *Recherches sur la force du cœur aortique*, Paris, 1828.

measures the height of the manometric column of mercury the downward pressure of which in one limb of the tube is just equal to the downward pressure of the fluid in the other. In order to adapt this "U-tube" to the study of the blood-pressure, that limb of the tube which is to communicate with the artery or vein is capped with a cock which can be closed. Into this same limb, a little way below the cock, opens at right angles a short straight glass tube, which is to communicate with the blood-vessel through a long flexible tube of lead, supported by the iron frame, and a short glass cannula tied into the blood-vessel itself. Two short pieces of india-rubber tube join the lead tube to the manometer and the cannula. Before the blood-vessel is connected with the manometer, the latter is filled with fluid between the surface of the mercury next the blood-vessel and the outer end of the lead tube, which fluid is such that when mixed with blood it prevents or greatly retards coagulation. With this same fluid the glass cannula in the blood-vessel is also filled, and then this cannula and the lead tube are connected. The cock at the upper end of the "proximal limb" of the manometer is to facilitate this filling, being connected by a rubber tube with a "pressure bottle," and is closed when the filling has been accomplished. The fluid introduced by Poiseuille and still generally used is a strong watery solution of sodium carbonate. A solution of magnesium sulphate is also good. If, in injecting this fluid, the column of mercury in the "distal limb" is brought to about the height which is expected to indicate the blood-pressure, but little blood will escape from the blood-vessel when the clamp is taken from it, and coagulation may not set in for a long time.

**The Recording Mercurial Manometer and the Graphic Method.**—When the arterial pressure is under observation, the combined respiratory and cardiac fluctuations of the mercurial column are so complex and frequent that it is very hard to read off their course accurately even with the help of a millimeter-scale placed beside the tube. In 1847 this difficulty led the German physiologist Carl Ludwig to convert the mercurial manometer into a self-registering instrument. This invention marked an epoch not merely in the investigation of the circulation, but in the whole science of physiology, by beginning the present "graphic method" of physiological work, which has led to an immense advance of knowledge in many departments. Ludwig devised the "recording manometer" by placing upon the mercury in the distal air-containing limb of Poiseuille's instrument an ivory float, bearing a light, stiff, vertical rod (see Fig. 15). Any fluctuation of the mercurial column caused float and rod to rise and fall like a piston. The rod projected well above the manometer, at the mouth of which a delicate bearing was provided to keep the motion of the rod vertical. A very delicate pen placed horizontally was fastened at right angles to the upper end of the rod. If a firm vertical surface, covered with paper, were now placed lightly in contact with the pen, a rise of the mercury would cause a corresponding vertical line to be marked upon the paper, and a succeeding fall would cause the descending pen to inscribe a second line covering the first. If now the vertical surface were made to move past the pen at a uniform rate,



the successive up-and-down movements of the mercury would no longer be marked over and over again in the same place so as to produce a single vertical line. The space and time taken up by each fluctuation would be graphically recorded in the form of a curve, itself a portion of a continuous trace marked by the successive fluctuations; thus both the respiratory and cardiac fluctuations could be registered throughout an observation by a single complex curving line. Ludwig stretched his paper around a vertical hollow cylinder of brass, made to revolve at a regular known rate by means of clock-work, and the conditions above indicated were satisfied<sup>1</sup> (see Fig. 15). Upon the surface of such a cylinder vertical distance represents space, and a vertical line of measurement is called, by an application of the language of mathematics, an "ordinate;" horizontal distance represents time, and a horizontal line of measurement is called an "abscissa." The curve marked by the events recorded is always a mixed record of space and time. The instrument itself, the essential part of which is the regularly revolving cylinder, is called the "kymograph."<sup>2</sup> It has undergone many changes, and many varieties of it are in use. Any motor may be used to drive the cylinder, provided that the speed of the latter be uniform and suitable.

The curve written by the manometer or other recording instrument may either be marked upon paper with ink, as in Ludwig's earliest work; or may be marked with a needle or some other fine pointed thing upon paper black-

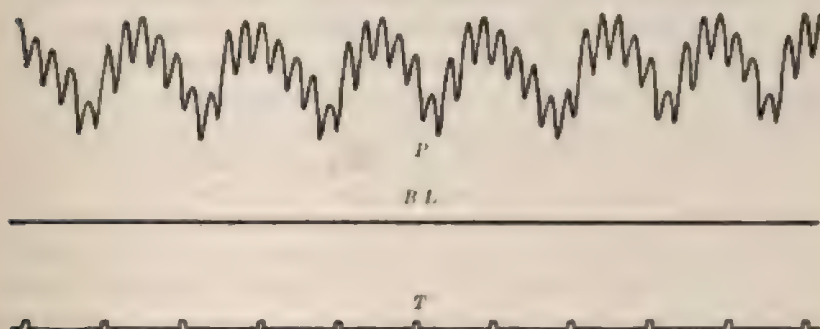


FIG. 16.—The trace of arterial blood-pressure from a dog anesthetized with morphia and ether. The cannula was in the proximal stump of the common carotid artery. The curve is to be read from left to right.

*P*, the pressure-trace written by the recording mercurial manometer;

*B L*, the base line or abscissa, representing the pressure of the atmosphere. The distance between the base-line and the pressure-curve varies, in the original trace, between 62 and 77 millimeters, therefore the pressure varies between 124 and 154 millimeters of mercury, less a small correction for the weight of the sodium-carbonate solution;

*T*, the time-trace, made up of intervals of two seconds each, and written by an electro-magnetic chronograph.

ened with soot over a flame. The trace written upon smoked paper is the more delicate. After the trace has been written, the smoked paper is removed from the kymograph and passed through a pan of shellac varnish. This

<sup>1</sup> C. Ludwig: "Beiträge zur Kenntnis des Einflusses der Respirationsbewegungen auf den Blutlauf im Aortensysteme," *Müller's Archiv für Anatomie, Physiologie, und wissenschaftliche Medizin*, etc., 1847, S. 242.

<sup>2</sup> From *cima*, a wave.



when dry fixes the trace, which thereafter will not be spoiled by handling. In Figure 16 the uppermost line shows a trace which fairly represents the successive fluctuations of the aortic pressure of the dog. The longer and ampler fluctuations are respiratory, the briefer and slighter are cardiac. In each respiratory curve the lowest point and the succeeding ascent coincide with inspiration; the highest point and the succeeding descent with expiration. The horizontal middle line is the base line, representing the pressure of the atmosphere. The base-line has been shifted upward in the figure simply in order to save room on the page. In the lowermost line the successive spaces from left to right of the reader represent successive intervals of time of two seconds each, written by an electro-magnetic chronograph. The pressure-trace taken from a vein may in certain regions near the chest show respiratory fluctuations, but nowhere cardiac ones, as the pulse is not transmitted to the veins. The venous pressure is so small, that for the practical study of it a recording manometer must be used in which some lighter fluid replaces the mercury, which would give a column of insufficient height for working purposes. The values obtained are then reduced by calculation to millimeters of mercury, for comparison with the arterial pressure. The intravascular pressure at a given moment can be measured by measuring a vertical line or "ordinate" drawn from the curve written by the manometer to the horizontal base-line. The latter represents the height of the manometric column when just disconnected from the blood-vessel; that is, when acted upon only by the weight of the atmosphere and of the solution of sodium carbonate. To ascertain the blood-pressure, the length of the line thus measured must be doubled; because the mercury in the proximal limb of the manometer sinks under the blood-pressure exactly as much as the float rises in the distal limb. A small correction must also be made for the weight of the solution of sodium carbonate.

**The Mean Pressure.**—The "mean pressure" is the average pressure during whatever length of time the observer chooses. The mean pressure for the given time is ascertained from the manometric trace by measurements too complicated to be explained here. As the weight and consequent inertia of the mercury cause it to fluctuate according to circumstances more or less than the pressure, the mean pressure is much more accurately obtained from the mercurial manometer than is the true height of each fluctuation, which is very commonly written too small. Therefore, it is especially the mean pressure that is studied by means of the mercurial manometer. The true extent and finer characters of the single fluctuations caused by the heart's beat are better studied with other instruments, as we shall see in dealing with the pulse.

It has been seen that the blood flows continuously through the capillaries because the pressure is continually high in the arteries and low in the veins. The reader is now in position to understand statements of the blood-pressure expressed in millimeters of mercury. The mean aortic pressure in the dog is far from being always the same even in the same animal. We have found it, in the case referred to on page 85, to be equivalent to about 121 millimeters of mercury. It will very commonly be found higher than this, and may range

up to, or above, 200 millimeters. In man it is probably higher than in the dog. The pressure in the other arteries derived from the aorta which have been studied manometrically is not very greatly lower than in that vessel. In the pulmonary arteries the pressure is probably much lower than in the aortic system. The pressure in the small veins of the head of the dog, the cannula being in the distal stump of the external jugular vein, we have found already in one case to equal about 14 millimeters of mercury. In such a case the presence of valves in the veins and other elements of difficulty make the mean pressure hard to obtain as opposed to the maximum pressure during the period of observation.

If a cannula be so inserted as to transmit the pressure obtaining within the great veins of the neck just at the entrance of the chest, without interfering with the movement of the blood through them, and if a manometer be connected with this cannula, the fluid will fall below the zero-point in the distal limb, indicating a slight suction from within the vein, and thus a slightly "negative" pressure.<sup>1</sup> This negative pressure may sometimes become more pronounced during inspiration and regain its former value during expiration. Sometimes, again, the pressure during expiration may become positive. The continuous flow from the great arteries through the capillaries to the veins, and through these to the auricle, is therefore shown by careful quantitative methods, no less than by the tube of Hales, to be simply a case of movement of a fluid from seats of high to seats of lower pressure.

**The Symptoms of Bleeding in Relation to Blood-pressure.**—The differences of pressure revealed scientifically by the manometer exhibit themselves in a very important practical way when blood-vessels are wounded and bleeding occurs. If an artery be cleanly cut, the high pressure within drives out the blood in a long jet, the length of which varies rhythmically with the cardiac pulse, but varies only to a moderate degree. From wounded capillaries, or from a wounded vein, owing to the low pressure, the blood does not spring in a jet, but simply flows out over the surface and drips away without pulsation. At the root of the neck, where the venous pressure may rhythmically fall below and rise above the atmospheric pressure, the bleeding from a wounded vein may be intermittent.

#### D. THE CAUSES OF THE PRESSURE IN THE ARTERIES, CAPILLARIES, AND VEINS.

The causes of the continuous high pressure in the arteries must first engage our attention.

**Resistance.**—The great ramification of the arterial system at a distance from the heart culminates in the formation of the countless arterioles on the confines of the capillary system. We have already seen direct evidence of the friction in the minute vessels which results from this enormous subdivision of the blood-path. The force resulting from this friction is propagated back-

<sup>1</sup> H. Jacobson: "Ueber die Blutbewegung in den Venen," *Reichert's und du Bois-Reymond's Archiv für Anatomie, Physiologie, etc.*, 1867, S. 224.



ward according to the laws of fluid pressure, and constitutes a strong resistance to the onward movement of the blood out of the heart itself. Friction is everywhere present in the vessels, but is greatest in the very small ones collectively.

**Power.**—Where the aorta springs from the heart, the rhythmic contractions of the left ventricle force open the arterial valve, and force intermittent charges of blood into the arterial system, overcoming thus the opposing force derived from friction. The wall of the arterial system is very elastic everywhere. Thus the high pressure in the arteries results from the interaction of the power derived from the heart's beat and the resistance derived from friction. That the high pressure is continuous depends upon the capacity for distention possessed by the elastic arterial wall.

**Balance of the Factors of the Arterial Pressure.**—In order to study the causation of the arterial pressure, let us imagine that it has for some reason sunk very low; but that, at the moment of observation, a normally beating heart is injecting a normal blood-charge into the aorta. The first injection would find the resistance of friction present, and the elastic arterial wall but little distended. For this injection some room would be made by the displacement of blood into the capillaries. But it would be easier for the arterial wall to yield than for the friction to be overcome, so the injected blood would largely be stored within the arterial system and thus raise the pressure. Succeeding injections would have similar results; it would continue to be easier for the injected blood to distend the arteries than to escape from them; and the arterial pressure would rise rapidly toward its normal height. Presently, however, a limit would be reached; a time would come when the elastic wall, already well stretched, would have become tenser and stiffer and would yield less readily before the entering blood; and now a larger part than before of each successive charge of blood would be accommodated by the displacement of an equivalent quantity into the capillaries, and a smaller part by the yielding of the arterial wall. Normal conditions of pressure would be reached and maintained when the blood accommodated, during each systole of the ventricle, by the yielding of the arterial wall should exactly equal in amount the blood discharged from the arteries into the capillaries during each ventricular diastole; for then the quantity of blood parted with by the arteries during both the systole and the diastole of the heart would be exactly the same as that received during its systole alone.

We see that, at each cardiac systole, the cardiac muscle does work in maintaining the capillary flow against friction, and also does work upon the arterial wall in expanding it. A portion of the manifest energy of the heart's beat thus becomes potential in the stretched elastic fibres of the artery. The moment that the work of expansion ceases, the stretched elastic fibres recoil; their potential energy, just received from the heart, becomes manifest, and work is done in maintaining the capillary flow against friction during the repose of the cardiac muscle. At the beginning of this repose the arterial valves have been closed by the arterial recoil. When, at each cardiac systole,



the arterial wall expands before the entering blood, the pressure rises, for more blood is entering the arterial system than is leaving it; when, at each cardiac diastole, the arterial wall recoils, the pressure falls, for blood is leaving the arterial system, and none is entering it. But before the fall has had time to become pronounced, while the arterial pressure is still high, the cardiac systole recurs, and the pressure rises again, as at the preceding fluctuation.

**The Arterial Pulse.**—The increased arterial pressure and amplitude at the cardiac systole, followed by diminished pressure and amplitude at the cardiac diastole, constitute the main phenomena of the arterial pulse. They are marked in the manometric trace by those lesser rhythmic fluctuations of the mercury which correspond with the heart-beats. The causes of the arterial pulse have just been indicated in dealing with the causes of the arterial pressure. The pulse, in some of its details, will be studied further for itself in a later chapter. For the sake of simplicity, the respiratory fluctuations of the arterial pressure have not been dealt with in the discussion just concluded. The causes of these important fluctuations are very complex and are treated of under the head of Respiration.

The arterial pressure, then, results from the volume and frequency of the injections of blood made by the heart's contraction; from the friction in the vessels; and from the elasticity of the arterial wall.

**The Capillary Pressure and its Causes.**—When we studied the movement of the blood in the capillaries, we found the pressure in them to be low and free from rhythmic fluctuations. In both of these qualities the capillary pressure is in sharp contrast with the arterial. What is the reason of the difference? The work of driving the blood through as well as into the capillaries is done during the contraction of the heart's wall by its kinetic energy. During the repose of the heart's wall and the arterial recoil this work is continued by kinetic energy derived, as we have seen, from the preceding cardiac contraction. The work of producing the capillary flow is done in overcoming the resistance of friction. The capillary walls are elastic. The same three factors, then—the power of the heart, the resistance of friction, the elasticity of the wall—which produce the arterial pressure produce the capillary pressure also. Why is the capillary pressure normally low and pulseless? The answer is not difficult. The friction which must be overcome in order to propel the blood out of the capillaries into the wider venous branches is only a part of the total friction which opposes the admission of the blood to the minuter vessels. The resistance is therefore diminished which the blood has yet to encounter after it has actually entered the capillaries. The force which propels the blood through the capillaries, although amply sufficient, is greatly less than the force which propels it into and through the larger arteries. In both cases alike the force is that of the heart's beat. But, in overcoming the friction which resists the entrance of the blood into the capillaries, a large amount of the kinetic energy derived from the heart has become converted into heat. The power is therefore diminished. As, in producing the high arterial pressure, much power is met by much resistance, and the elastic wall

is, therefore, distended with accumulated blood ; so, in producing the low capillary pressure, diminished power is met by diminished resistance, outflow is relatively easy, accumulation is slight, and the elasticity of the delicate wall is but little called upon.

**The Extinction of the Arterial Pulse.**—But why is the capillary pressure pulseless, as the microscope shows ? To explain this, no new factors need discussion, but only the adjustment of the arterial elasticity to the intermittent injections from the heart and to the total friction which opposes the admission of blood to the capillaries. This adjustment is such that the recoil of the arteries displaces blood into the capillaries during the ventricular diastole at exactly the same rate as that produced by the ventricular contraction during the ventricular systole. Thus, through the elasticity of the arteries, the cardiac pulse undergoes extinction ; and this becomes complete at the confines of the capillaries. The respiratory fluctuations become extinguished also, and the movement of the blood in the capillaries exhibits no rhythmic changes. This conversion of an intermittent flow into one not merely continuous but approximately constant affords a constant blood-supply to the tissues, at the same time that the cardiac muscle can have its diastolic repose, and the ventricular cavities the necessary opportunities to receive from the veins the blood which is to be transferred to the arteries.

A simple experiment will illustrate the foregoing. Let a long india-rubber tube be taken, the wall of which is thin and very elastic. Tie into one end of the tube a short bit of glass tubing ending in a fine nozzle, the friction at which will cause great resistance to any outflow through it. Tie into the other end of the rubber tube an ordinary syringe-bulb of india-rubber, with valves. Expel the air, and inject water into the tube from the valved bulb by alternately squeezing the latter and allowing it to expand and be filled from a basin. The rubber tube will swell and pulsate, but if its elasticity have the right relation to the size of the fine glass nozzle and to the amplitude and frequency of the strokes of the syringe, a continuous and uniform jet will be delivered from the nozzle, while the injections of water will, of course, be intermittent.

**The Venous Pressure and its Causes.**—The pressure in the peripheral veins is less than in the capillaries and declines as the blood reaches the larger veins. Very close to the chest the pressure is below the pressure of the atmosphere, and may sometimes vary from negative to positive, following the rhythm of the breathing. These respiratory fluctuations will be considered later. The low and declining pressures under which the blood moves through the venules and the larger veins are due to the same causes as those which account for the capillary pressure. It is still the force generated by the heart's contractions, and made uniform by the elastic arteries, which drives the blood into and through the veins back to the very heart itself. As the blood moves through the veins, what resistance it encounters is still that of the friction ahead. But the friction ahead is progressively less ; the conversion of kinetic energy into heat is progressively greater. The venous wall possesses elas-



ticity, but this is even less called upon than that of the capillaries; and, presently, in the larger veins, the moving blood is found to press no harder from within than the atmosphere from without.

**Subsidiary Forces which Assist the Flow in the Veins.**—There are certain forces which, occasionally or regularly, assist the heart to return the venous blood into itself. Too much stress is often laid upon these; for it is easy to see by experiment that the heart can maintain the circulation wholly without help. The origins of these subsidiary forces are, first, the contraction of the skeletal muscles in general; second, the continuous traction of the lungs; third, the contraction of the muscles of inspiration.

**The Skeletal Muscles and the Venous Valves.**—A vein may lie in such relation to a muscle that when the latter contracts the vein is pressed upon, its feeble blood-pressure is overborne, the vein is narrowed, and blood is squeezed out of it. The veins in many parts are rich in valves, competent to prevent regurgitation of the blood while permitting its flow in the physiological direction. The pressure of a contracting muscle, therefore, can only squeeze blood out of a vein toward the heart, never in the reverse direction. Muscular contraction, then, may, and often does, assist in the return of the venous blood with a force not even indirectly derived from the heart. But such assistance, although it may be vigorous and at times important, is transient and irregular. Indeed, were a given muscle to remain long in contraction, the continued squeezing of the vein would be an obstruction to the flow through it.

**The Continuous Pull of the Elastic Lungs.**—The influence of thoracic aspiration upon the movement of the blood in the veins deserves a fuller discussion. The root of the neck is the region where this influence shows itself most clearly, but it may also be verified in the ascending vena cava of an animal in which the abdomen has been opened. The physiology of respiration shows that not only in inspiration, but also in expiration, the elastic fibres of the lungs are upon the stretch, and are pulling upon the ribs and intercostal spaces, upon the diaphragm, and upon the heart and the great vessels. This dilating force at all times exerted upon the heart by the lungs is of assistance, as we shall see, in the diastolic expansion of its ventricles. In the same way the elastic pull of the lungs acts upon the venæ cavæ within the chest, and generates within them, as well as within the right auricle, a force of suction. The effects upon the venous flow of this continuous aspiration are best known in the system of the descending vena cava. This suction from within the chest extends to the great veins just without it in the neck. In these, close to the chest, as we have seen, manometric observation reveals a continuous slightly negative pressure. A little farther from the chest, however, but still within the lower portions of the neck, the intravenous pressure is slightly positive. The elastic pull of the lung, therefore, continuously assists in unloading the terminal part of the venous system, and thus differs markedly from the irregular contractions of the skeletal muscles.

**The Contraction of the Muscles of Inspiration.**—But some skeletal



muscles, those of inspiration, regularly add their rhythmic contractions to the continuous pull of the lungs, to reinforce the latter. Each time that the chest expands there is an increased tendency for blood to be sucked into it through the veins. At the beginning of each expiration this increase of suction abruptly ceases.

**The Respiratory Pulse in the Veins near the Chest, and its Limitation.**—In quiet breathing the movements of the chest-wall produce no very conspicuous effect. If, however, deep and infrequent breaths be taken, the pressure within the veins close to the chest becomes at each inspiration much more negative than before; and at each inspiration the area of negative pressure may extend to a greater distance from the chest along the veins of the neck, and perhaps of the axilla. As the venous pressure in these parts now falls as the chest rises, and rises as the chest falls, a visible venous pulse presents itself, coinciding, not with the heart-beats, but with the breathing. At each inspiration the veins diminish in size, as their contents are sucked into the chest faster than they are renewed. At each expiration the veins may be seen to swell under the pressure of the blood coming from the periphery. If the movements of the air in the windpipe be mechanically impeded, these changes in the veins reach their highest pitch; for then the muscles of expiration may actually compress the air within the lungs, and produce a positive pressure within the vena cava and its branches, with resistance to the return of venous blood during expiration, shown by the swelling of the veins. These phenomena are suddenly succeeded by suction, and by collapse and disappearance of the veins, as inspiration suddenly recurs. The respiratory venous pulse, when it occurs, diminishes progressively and rapidly as the veins are observed farther and farther from the root of the neck—a fact which results from the flaccidity of the venous wall. Were the walls of the veins rigid, like glass, the successive inspirations would produce obvious accelerations of the flow throughout the whole venous system, and the contractions of the muscles of inspiration would rank higher than they do among the causes of the circulation. In fact, the walls of the veins are very soft and thin. If, therefore, near the chest, the pressure of the blood within the veins sinks below that of the atmosphere, the place of the blood sucked into the chest is filled only partly by a heightened flow of blood from the periphery, but partly also by the soft venous wall, which promptly sinks under the atmospheric pressure. This is shown by the visible flattening, perhaps disappearance from view, of the vein. This process reduces the visible venous pulse, where it occurs, to a local phenomenon; for, at each inspiration, the promptly resulting shrinkage of all the affected veins together is nearly equivalent to the loss of volume due to the sucking of blood into the chest. Therefore the flow in the more peripheral veins remains but slightly affected, and the pressure within them continues to be positive and without a visible pulse. During expiration the swelling of the veins near the chest, the return of positive pressure within them, may be simply from the return of the ordinary balance of forces after the effects of a deep inspiration have

disappeared. But, if expiration be violent and much impeded, the positive pressure may rise much above the normal. Here again, however, regurgitation will meet with opposition from the venous valves, though the flow from the periphery may be much impeded.

**The "Dangerous Region," and the Entrance of Air into a Wounded Vein.**—Quite close to the chest, then, the normal venous pressure is always slightly negative; and in deep inspiration it may become more so, and this condition may extend farther from the chest along the neck and axilla, throughout a region known to surgeons as "the dangerous region." It is important to understand the reason for this expression. It has already been mentioned that the wounding of a vein in this region may cause intermittent bleeding. It now will easily be understood that such bleeding will occur only when the pressure is positive—that is, during expiration. During deep and difficult breathing, indeed, the venous blood may spring in a jet during expiration instead of merely flowing out, and may wholly cease to flow during inspiration. The cessation is due, of course, to the blood being sucked into the chest past the wound rather than pressed out of it.

It is not, however, the risks of hemorrhage that have earned the name of "dangerous" for the region where intermittent bleeding may occur. The danger referred to is of the entrance of air into the wounded vein and into the heart,—an accident which is commonly followed by immediate death, for reasons not here to be discussed. Very close to the chest, where the venous pressure is continuously negative and the veins are so bound to the fasciæ that they may not collapse, this danger is always present. Throughout the rest of the dangerous region, the entrance of air into a wounded vein will take place only exceptionally. In quiet breathing the venous pressure is continuously positive throughout most of this region; and then a wounded vein will merely bleed. It is only in deep breathing that a venous pulse becomes visible here, and that the venous pressure becomes negative in inspiration. But even in forced breathing it is rare for a wounded vein of the dangerous region to do more than bleed. The cause of this lies in the flaccidity of the venous wall. At each expiration the blood may jet from the wound; but at the following deep inspiration the weight of the atmosphere flattens the vein so promptly that the blood is followed down by the wounded wall and no air enters at the opening. It is only when, during deep breathing, the wounded wall for some reason cannot collapse, that the main part of the "dangerous region" justifies its name. Should the tissues through which the vein runs have been stiffened by disease, or should the wall of the vein adhere to a tumor which a surgeon is lifting as he cuts beneath it, in either case the vein will have become practically a rigid tube. Should it be wounded during a deep inspiration, blood will be sucked past the wound, but the atmospheric pressure will fail to make the wall collapse; air will be drawn into the cut, and blood and air will enter the heart together, probably with deadly effect.

**Summary.**—It appears from what has gone before that the elasticity of the lungs and the contractions of the muscles of inspiration regularly assist in



unloading the veins in the immediate neighborhood of the heart, and so remove some part of the resistance to be overcome by the contractions of the cardiac muscle. When we come to the detailed study of the heart it will appear also that a slight force of suction is generated by the heart itself, which force adds its effects upon the flow of venous blood to those of the elasticity of the lungs and of the contraction of the muscles of inspiration.

It must here be repeated, however, that the heart is quite competent to maintain the circulation unaided. This is proven as follows: If in an anæsthetized mammal a cannula be placed in the windpipe, the chest be widely opened, and artificial respiration be established, the circulation, though modified, continues to be effective. By the opening of the chest its aspiration has been ended, and can no longer assist in the venous return. If, further, the animal be drugged in such a manner as completely to paralyze the skeletal muscles throughout the body, their contractions can exert no influence upon the venous return; yet the circulation is still kept up by the heart, unaided either by the elasticity of the lungs, by the contractions of the muscles which produce inspiration, or by those of any other skeletal muscles.

#### E. THE SPEED OF THE BLOOD IN THE ARTERIES, CAPILLARIES, AND VEINS.

If we keep as our text, in discussing the circulation, the character of the capillary flow, it will be seen that we have now accounted for the facts that the capillary flow is toward the veins; that it shows much friction; that it is continuous, pulseless, and under low pressure. We have not yet accounted for the fact that it is slow. We must now do so, but must first state and account for the speed of the blood in the arteries and veins.

**The Measurement of the Blood-speed in Large Vessels; the "Stromuhr."**—The speed of the blood in the larger veins and arteries must be measured indirectly. We can picture to ourselves the volume of blood which moves past a given point in a given blood-vessel in one second, as a cylinder of blood having the same diameter as the interior of the blood-vessel. The length of this cylinder will then be expressed by the same number which will express the velocity with which a particle of the blood would pass the given point in one second, provided that this velocity be uniform and be the same for all the particles. In order, then, to learn the average speed of the blood at a given point of an artery or vein during a certain number of seconds, we have only to measure the calibre of the blood-vessel and the quantity of blood which passes the selected point during the period of observation. From these two measurements the speed can be obtained by calculation. But these two measurements are not quite easy. The physical properties of the blood-vessels, especially of the veins, make their calibres variable and hard to estimate justly as affected by the conditions present during an experiment. The means adopted for measuring the quantity of blood passing a point in a given time necessarily alters the resistance encountered by the flow, and so of itself affects both the rate of flow and the blood-pressure; and, with the



latter, the calibre of the vessel. For these reasons any measurement of the average speed of the blood by the above method is only approximately correct. The best instrument for measuring the quantity of blood driven past a point during an experiment is the so-called "stromuhr" or "rheometer" of Ludwig, a longitudinal section of which is given diagrammatically in Figure 17.<sup>1</sup> This is essentially a curved tube shaped like the Greek capital letter  $\alpha$ . Each end of the tube is tied into one of the two stumps (*a* and *b*) of the divided vessel. These ends of the tube are as nearly as possible of the same calibre as the vessel selected. Each limb of the tube is dilated into a bulb, and the upper part of the tube, including the two bulbs, is of glass; the lower part of each limb is of metal. At the top, between the bulbs, is an opening for filling the tubes, which can easily be closed when not in use. Each end of the tube is filled with defibrinated blood before being tied into the blood-vessel. In the limb of the tube (*B*,

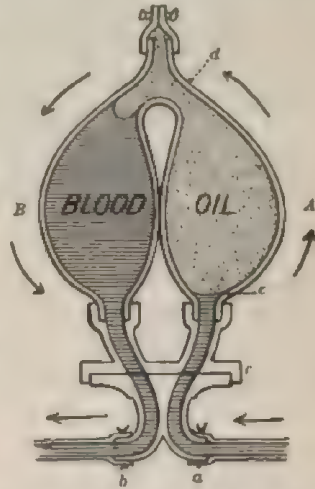


FIG. 17.—Diagram of longitudinal section of Ludwig's "Stromuhr." The arrows mark the direction of the blood-stream. For further description see the text.

(Fig. 17) which is the farther from the heart if an artery be used, or the nearer to the heart if a vein, the defibrinated blood is made to fill the cavity up to the top of the bulb. In the other limb (*A*, Fig. 17) the blood fills the tube only up to a mark (*c*, Fig. 17) near the bottom of the bulb. Through the opening between the bulbs the still vacant space, which includes the whole of the bulb *A*, is filled with oil, all air being excluded. The opening is then closed. If now the clamps be removed from the blood-vessel, the blood of the animal will enter the tube at *a* and drive before it the contents of the tube. Thus defibrinated blood from *B* will be driven into the distal stump of the vessel at *b*, and will enter the circulation of the animal. Oil will at the same time be driven over from *A* to *B*. The bulb *A* has upon it two marks, *d* and *e*, one near the top of it, the other near the bottom. The instant when the line between the oil and the advancing blood reaches the mark near the top of *A* is the instant when a volume of blood equal to that of the displaced oil has entered *A*, past the mark near the bottom of it. The capacity of the tube between the two marks is accurately known. The time required for this space to be filled with the entering blood is measured by the observer. The calibre of the metal tube at *a* is accurately known, and is assumed to be equal to the calibre of the blood-vessel. From these measurements the average speed of the blood-stream at *a* is calculated.

<sup>1</sup> J. Dogiel: "Die Ausmessung der strömenden Blutvolumina," *Berichte über die Verhandlungen der k. sächsischen Gesellschaft der Wissenschaften zu Leipzig, Math.-physische Classe*, 1887, s. 200.

The metallic lower part of the instrument, which includes both limbs of the tube, is completely divided horizontally at *c*. The two parts are so built, however, as to be maintained in water-tight apposition. This arrangement permits the whole upper part of the instrument, including the glass bulbs, to be rotated suddenly upon the lower, so that the bulb *B* may correspond with the entrance for the blood at *a*, and the bulb *A* with the exit for the blood at *b*. If this rotation be effected at the instant when the space between the two marks on *A* has been filled with blood, the bulb *B*, now charged with oil, will be filled by the blood which enters next, and the first charge of the animal's own blood will make its exit at *b*. Oil will now pass over from *B* to *A*; when the line between it and the blood which is leaving *A* has just reached the lower mark on *A*, the bulbs are turned back to their original position. Thus, by repeated rotations, each of which can be made to record upon the kymograph the instant of its occurrence, a number of charges of blood can be received and transmitted in succession; it is always the same space, between the marks on *A*, which is used for measuring the charge; and the time of the experiment can be much prolonged. By this procedure the errors due to a single brief observation can be greatly reduced. Indeed, the time of entrance of a single charge of blood would be quite too short to give a satisfactory result.

The use of the stromuhr not only affords necessary data for the calculation of the average speed of the blood, but seeks directly to measure the volume of blood delivered in a given time by an artery to its capillary district. It is evident that this volume is a quantity of fundamental importance in the physiology of the circulation. Could we ascertain it, by direct measurement or by calculation, for the aorta or pulmonary artery, we should know at once the volume of blood delivered to the capillaries in one second, and thus the time taken for the entire blood to enter either those of the lungs or of the system at large. By this knowledge, many important problems would be advanced toward solution.

**The Measurement of Rapid Fluctuations of Speed.**—The stromuhr can give only the average speed of the blood during the experiment. To study rapid fluctuations of speed, another method is needed. If, in a large animal, a vessel, best an artery, be laid bare, a needle may be thrust into it at right angles. If the needle be left to itself, the end which projects from the artery will be deflected toward the heart, because the point will have been deflected toward the capillaries by the blood-stream. The angle of deflection might be read off, could a graduated semicircle be adjusted to the needle. If the stream be arrested, the needle returns to its position at right angles to the artery. The greater the velocity of the stream, the greater is the deflection of the needle. If, later, the same needle be thrust into a tube of rubber through which water flows at known rates of speed, the speed corresponding to each angle of deflection of the needle may be determined. If the needle were made to mark upon a kymograph, variations of the speed would be recorded as a curve.



An instrument based on the principles just described is valuable for the study of rapid changes of velocity.<sup>1</sup> In an artery, its needle oscillates rhythmically, showing that there the speed of the blood varies during each beat of the heart, being greatly accelerated by the systole of the ventricle, and retarded by the cessation of the systole. It will be remembered that the microscope directly shows faint rhythmic accelerations in the minute arteries of the frog. In the veins rhythmic changes of speed do not occur except near the heart from respiratory causes.

**The Speed of the Blood in the Arteries.**—The stromuhr shows that the speed of the blood is liable to great variations. This fact, and the range of speed in the arteries, are fairly exhibited by the results obtained by Dogiel from the common carotid artery of a dog, the experiment upon which lasted 127 seconds. During this time six observations were made which varied in length from 14 to 30 seconds each. For one of these periods the average speed was 243 millimeters in one second; for another period, 520 millimeters. These were the extremes of speed noted in this case.<sup>2</sup> The speed in the arteries diminishes toward the capillaries.

**The Speed of the Blood in the Veins.**—The speed in a vein tends to be slower than that in an artery of about the same importance, but is not necessarily so.<sup>3</sup> It increases from the capillaries toward the heart.

**The Speed of the Blood in the Capillaries.**—The rate of the capillary flow may be measured directly under the microscope. Certain physiologists have also observed the movement of the blood in the retinal capillaries of their own eyes, and have measured its rate there.<sup>4</sup> Both methods show that in the capillaries the speed is very much less than in the large arteries or large veins. In the capillaries of the web of the frog's foot it is only about 0.5 millimeter in one second. In those of the mesentery of a young dog it has been found to be 0.8 millimeter; in those of the human retina, from 0.6 to 0.9 millimeter.

**Speed and Pressure of the Blood Compared.**—If now we compare the speed with the pressure of the blood in the arteries, in the capillaries, and in the veins, we shall be struck by both similarities and differences. In the arteries both pressure and speed rhythmically rise and fall together; and both the mean pressure and the mean speed decline from the heart to the capillaries. In the capillaries both pressure and speed are pulseless and low,—very low compared with the great arteries. In the veins, however, the pressure is everywhere lower than in the capillaries and falls from the capillaries to the heart; the speed is everywhere higher than in the capillaries and rises from

<sup>1</sup> M. L. Lortet: *Recherches sur la vitesse du cours du sang dans les artères du cheval au moyen d'un nouvel hémodynamographe*, Paris, 1867.

<sup>2</sup> J. Dogiel: *loc. cit.*

<sup>3</sup> E. Cyon und F. Steinmann: "Die Geschwindigkeit des Blutstroms in den Venen," *Bulletin de l'Académie Impériale des Sciences de St. Pétersbourg*, 1871; also in E. Cyon: *Gesammelte physiologische Arbeiten*, 1888. S. 110.

<sup>4</sup> K. Vierordt: *Die Erscheinungen und Gesetze der Stromgeschwindigkeiten des Blutes*, etc., 1862, S. 41, 111.



the capillaries to the heart. It is apparent, therefore, that there is no direct connection between the pressure and the speed of the blood at a given point, inasmuch as they change together along the arteries and change inversely along the veins. How varied the combinations may be of pressure and speed will be seen in studying the regulation of the circulation.

In the great veins, as in the arteries, the speed is very high compared with the capillaries. In the capillaries the speed of the blood is least, while in the tubes which supply and which drain them the speed is great. The physiological value of these facts is clear. It has already been pointed out that the blood moves slowly through the short and narrow tubes, where its exchanges with tissue and with air are effected, and swiftly through the long tubes of communication. What are the physical conditions which underlie these physiological facts?

**The speed of the blood varies inversely as the collective sectional area of its path.** If the circulation in an animal continue uniform for a time—during several breaths and heart-beats—it is evident that the forces concerned must be so balanced that, during that time, equal quantities of blood will have entered and left the heart, the arteries, the capillaries, and the veins, respectively. If the arteries, for instance, lose more blood than the heart transmits to them, this blood must accumulate in the veins till the arteries become drained and the supply to the capillaries fails. The very maintenance of a circulation, then, implies that equal quantities of blood must pass any two points of the *collective* blood-path in equal times, except when a general readjustment of the rate of flow may lead to a temporary disturbance of it. It will be seen at once that this principle is consistent with the widest differences of rate between individual arteries of the same importance, or between individual veins or capillaries. If in one artery the flow be increased by one-half, and in another be diminished by one-half, the total flow in the two arteries collectively will be the same as before.

If the principle just stated be considered in connection with the anatomy of the blood-path, the differences of speed in the arterial, capillary, and venous systems will at once be understood. The wider arteries and veins are few. Dissection shows that when an artery or vein divides, the calibre, and, with the calibre, the “sectional area” of the branches taken together, is commonly larger than that of the parent trunk. In general it is a law of the arterial and venous anatomy that the collective sectional area of the vessels of either system increases from the heart to the capillaries. The smaller the individual vessels are, the wider is the blood-path which they make up collectively. Widest of all is the blood-path where the individual vessels are smallest—that is, in the capillary system. The collective sectional area of the capillaries is several hundred times that of the root of the aorta. The collective sectional area of the veins which enter the right auricle is greater, perhaps twice as great, as that of the root of the aorta. The venous system, regarded as a single tube, is of much greater calibre than the arterial. It is perhaps better to make these general statements than to compare the different figures given

by different observers. The arterial and venous systems, treated as each a single tube, may be compared roughly to two funnels, each having its narrow end at the heart. The very wide and very short single tube of the capillary system may be imagined to connect the wide ends of the two funnels. Equal quantities of blood pass in equal times any two points of the collective blood-path between the left ventricle and the right auricle. Therefore where the blood-path is wide, these quantities must move slowly, and swiftly where the blood-path is narrow. It is owing, then, to the rapid widening of the arterial path that the speed declines, like the pressure, toward the capillaries. It is owing to the huge relative calibre of the path at the capillaries that in them the speed is by far the least while the same volume is passing that passes a point in the narrow aorta in the same time; it is owing to the steady narrowing of the venous path toward the heart that the venous blood is constantly quickening its speed while its pressure is falling. As the calibre of the venous system is greater than that of the arterial, the average speed in the veins is probably less than in the arteries. As the collective calibre of the veins which enter the right auricle is greater than that of the aorta, the blood probably moves into the heart less swiftly than out of it; though of course equal quantities enter and leave it in equal times provided those times are not mere fractions of a beat. In connection with this it is significant that the entrance of blood into the heart takes place during the long auricular diastole, while its exit is limited to the shorter ventricular systole.

**Time Spent by the Blood in a Systemic Capillary.**—The width of the path, then, determines the slow movement of the blood in the areas where it is fulfilling its functions; the narrowness of the path, the swiftness of movement of the blood in leaving and returning to the heart. We have seen (p. 79) that a particle of blood may make the entire round of a dog's circulation in from fifteen to eighteen seconds. If we assume the systemic capillary flow to be at the rate of 0.8 millimeter in one second, the blood would remain about 0.6 of a second in a systemic capillary half a millimeter long. Slow as is the capillary flow, it thus appears that it is none too slow to give time for the uses of the blood to be fulfilled.

#### F. THE FLOW OF BLOOD THROUGH THE LUNGS.

The blood moves from the right ventricle to the left auricle under the same general laws as from the left ventricle to the right auricle. Certain differences, however, are apparent, and must be noted. One difference is that the collective friction is less in the pulmonary than in the systemic vessels, and that therefore the resistance to be overcome by each contraction of the right ventricle is less than that opposed to the left ventricle. Accordingly it appears from dissection that the muscular wall of the right ventricle is much thinner than that of the left. No accurate measurements can be made of the normal pressure and speed of the blood in the arteries, capillaries, and veins of the lungs, because they can be reached only by opening the chest and destroying the mechanism of respiration, and thereby disturbing the normal



conditions of the pulmonary blood-stream. In the opened chest these cannot be entirely restored by artificial respiration. The thinness of the wall of the pulmonary artery, however, indicates that it has much less pressure to support than that of the aorta, which fact also is indicated by such roughly approximate results as have been obtained with the manometer after opening the chest.

As the pulmonary artery and veins lie wholly within the chest, but outside the lungs, their trunks and larger branches all tend to be dilated continuously by the elastic pull of the lungs—a pull which increases at each inspiration. On the other hand, the pulmonary capillaries lie so close to the surface of each lung that they are exposed to the same pressure, practically, as that surface, and the full weight of the atmosphere may act upon them. These conditions all tend to unload the capillaries and the pulmonary veins, but to weaken the unloading of the pulmonary artery. The two effects can hardly balance one another, however. The wall of the pulmonary artery is so much stiffer than that of the vein, that the actual results should be favorable to the flow. The elasticity of the lungs and the contractions of the muscles of inspiration thus lighten, probably, the work of the right ventricle as well as of the left. The right ventricle, however, like the left, can accomplish its work without assistance; for the entire circulation, including, of course, the flow through the lungs, continues after the chest has been opened, if artificial respiration be maintained.

#### G. THE PULSE-VOLUME AND THE WORK DONE BY THE VENTRICLES OF THE HEART.

**The Cardiac Cycle.**—It is assumed that the anatomy of the heart is known to the reader.

The general nature and effects of the heart's beat have been sketched already. Each beat has been seen to comprise a number of phenomena, which occur in regular order, and which recur in the same order during each of the succeeding beats. Each beat is therefore a cycle; and the phrase "cardiac cycle" has become a technical expression for "beat," as it conveys, in a word, the idea of a regular order of events. As each of the four chambers of the heart has its own systole and diastole, there are eight events to be studied in connection with each cycle. The systoles of the two auricles, however, are exactly simultaneous, as are their diastoles; and the same is true of the systoles and of the diastoles of the two ventricles. We may, therefore, without confusion, speak of the auricular systole and diastole, and of the ventricular systole and diastole, as of four events, each involving the narrowing or widening of two chambers, a right and a left. The heart of the mammal or bird consists essentially of a pair of pumps, the ventricles, each of which acts alternately as a powerful force-pump and as a very feeble suction-pump. To each ventricle is superadded a contractile appendage, the auricle, through which, and to some extent by the agency of which, blood enters the ventricle.



**The Pulse-volume.**—The central fact of the circulation of the blood is the injection, at intervals, by each ventricle, against a strong resistance, of a charge of blood into its artery, which charge the ventricle has just received out of its veins through its auricle. This quantity must be exactly the same for the two ventricles under normal conditions, or the circulation would soon come to an end by the accumulation of the blood in either the pulmonary or the systemic vessels. The blood ejected from each ventricle during the systole must also be equal in volume to the blood which enters each set of capillaries, the pulmonary or systemic, during that systole and the succeeding diastole of the ventricles, provided the circulation be proceeding uniformly. The quantity just referred to is called the "contraction volume" or "pulse-volume" of the heart. Were it always the same, and could we measure it, we should possess the key to the quantitative study of the circulation.

The pulse-volume may vary in the same heart at different times, as is easily shown by opening the chest, causing the conditions of the circulation to change, and noting that under certain conditions the heart during each beat varies in size more than before. This variation of volume is easily possible because the walls of the heart are of muscle, soft and distensible when relaxed. It is probable that at no systole is the ventricle quite emptied; that most of its cavity may become obliterated by the coming together of its walls, but that a space remains, just below the valves and above the papillary muscles, which is not cleared of blood. It is also probable that not only the blood which is ejected at the systole may vary in amount, but also the residual blood which remains in the ventricle at the end of the systole.<sup>1</sup> It is therefore clear that it is useless to attempt the measurement of the pulse-volume by measuring the fluid needed to fill the ventricle, even if the heart be freshly excised from the living body and injected under the normal blood-pressure. Rough approximations to this measurement may, however, be attempted in at least two ways:

In the first place, a modification of the stromuhr has been applied successfully to the aorta of the rabbit, between the origins of the coronary arteries and of the innominate. This operation requires that the auricles be clamped temporarily so as to stop the flow of blood into the ventricles, and to permit the aorta in its turn to be clamped and divided between the clamp and the ventricle, without serious bleeding. After the circulation has been re-established, the volume of the blood which passes through the instrument during the experiment, divided by the number of the heart-beats during the same period, gives the pulse-volume. The average result obtained, for the rabbit,

<sup>1</sup> F. Hesse: "Beiträge zur Mechanik der Herzbewegung," *Archiv für Anatomie und Physiologie* (anatomische Abtheilung), 1880, S. 328. C. Sandborg und W. Müller: "Studien über den Mechanismus des Herzens," *Pflüger's Archiv für die gesammte Physiologie*, 1880, xxii. S. 408. C. S. Roy and J. G. Adami: "Contributions to the Physiology and Pathology of the Mammalian Heart," *Proceedings of the Royal Society of London*, 1891-92, i. p. 435. J. E. Johanson und R. Tigerstedt: "Ueber die gegenseitigen Beziehungen des Herzens und der Gefässe;" "Ueber die Herzthätigkeit bei verschieden grossem Widerstand in den Gefässen," *Skandinavisches Archiv für Physiologie*, 1891, ii. S. 409.

is a volume of blood the weight of which is 0.00027 of the weight of the animal.<sup>1</sup>

A second way of attempting to ascertain the pulse-volume is to measure the swelling and the shrinkage of the heart. This is called the "plethysmographic"<sup>2</sup> method. One application of it is as follows: The chest and pericardium of an animal are opened, and the heart is inserted into a brass case full of oil. The opening through which the great vessels pass is made water-tight by mechanical means which do not impede the movement of the blood into and out of the heart. The top of the brass case is prolonged into a tube, the oil in which rises as the heart swells and falls as it shrinks. Upon the oil a light piston moves up and down, and records its movements upon the kymograph. The instrument is called a "cardiometer."<sup>3</sup>

The average pulse-volume of the human ventricle has been very variously estimated upon the basis of observations of various kinds made upon mammals of various species. The figures offered range, in round numbers, from 50 to 190 cubic centimeters. If we assume the human pulse-volume to weigh 100 grams, and the blood of a man who weighs 69 kilograms to weigh 5.308 kilograms, or  $\frac{1}{73}$  of his body-weight, the pulse-volume will be about  $\frac{1}{73}$  of the entire blood, and the entire blood will pass through the heart, from the veins to the arteries, in only fifty-three beats—that is, in less than one minute. The speed with which a man may bleed to death if a great artery be severed is therefore not surprising.

**The Work done by the Contracting Ventricles.**—Uncertain as is this important quantity of the pulse-volume, the estimation of the work done by the heart in maintaining the circulation must be based upon it, and upon the force with which each ventricle ejects the pulse-volume. A small fraction of this force is expended in imparting a certain velocity to the ejected blood; all the rest serves to overcome a number of opposing forces. The force exerted by the muscular contraction is opposed by the weight of the volume ejected, and by the strong arterial pressure, which resists the opening of the semilunar valve and the ejection of the pulse-volume. Moreover, the elasticity of the lungs tends at all times to dilate the ventricles, with a force which is increased at each recurring contraction of the muscles of inspiration. Probably there is also in the wall of the ventricle itself a slight elasticity which must be overcome by the ventricle's own contraction in order that its cavity may be effaced. The strong arterial pressure, with which the reader is already familiar, is by far the greatest of these resisting forces—in fact, is the only one of them which is not of small importance in the present connection.

Are we obliged to measure the force of the systole indirectly? Can we not ascertain it by direct experiment? Manometers of various kinds have been placed in direct communication with the cavities of the ventricles. The fol-

<sup>1</sup> W. Figszstedt, "Studien über die Blutvertheilung im Körper." Erste Abhandlung. "Bestimmung der von dem linken Herzen herausgetriebenen Blutmenge," *Skandinavisches Archiv für Physiologie*, 1891, iii 8, 145.

<sup>2</sup> From *plethysmos*, enlargement.

<sup>3</sup> C. S. Roy and J. G. Adami, *op. cit.*



lowing method, among others, has been employed: A tube open at both ends is introduced through the external jugular vein of an animal into the right ventricle, or, with greater difficulty, through the carotid artery into the left ventricle. In neither case is the valve, whether tricuspid or aortic, rendered incompetent during this proceeding, nor need the general mechanism of the heart and vessels be gravely disturbed. If the outer end of the tube be connected with a recording mercurial manometer, a tracing of the pressure within the right or left ventricle may be written upon the kymograph. It is found, however, that the pressure within the heart varies so much and so rapidly that the inert mercurial column will not follow the fluctuations, and that the attempt to learn the mean pressure by this method fails. A valve, however, may be intercalated in the tube between the ventricle and the manometer—a valve so made as to admit fluid freely to the manometer, but to let none out. The manometer will then record, and record not too incorrectly, the maximum pressure within the right or left ventricle during the experiment; in other words, it will record the greatest force exerted during that time by the ventricle in order to do its work.<sup>1</sup> In this way the maximum pressure within the left ventricle of the dog has been found to present such values as 176 and 234 millimeters of mercury, the corresponding maximum pressure in the aorta being 158 and 212 millimeters respectively.<sup>2</sup> The maximum pressures obtained from simultaneous observations upon the right and left ventricle of a dog are variously reported. It would perhaps be not far wrong to say that in this animal the pressure in the right ventricle is to that in the left as 1 to 2.6.<sup>3</sup>

The work done by each ventricle during its systole is found by multiplying the weight of the pulse-volume ejected into the force put forth in ejecting it. That force is equal to the pressure under which the pulse volume is expelled. If we use as a basis of calculation the pressures observed in the dog's heart with the maximum manometer, we may assume as the measure of a given pressure within the contracting human left ventricle 200 millimeters of mercury, and for the human right ventricle 77 millimeters. If for each column of mercury there be substituted the corresponding column of blood, the heights will be 2.567 meters and 0.988 meter respectively. The force exerted by the right or left ventricle upon the pulse-volume might therefore just equal that put forth in lifting it to a height of 0.988 or 2.567 meters. If we assume 100 grams as the weight of a possible pulse-volume ejected by a human ventricle, the work done at each systole of the left ventricle would be  $100 \times 2.567 = 256.7$  gram-meters, and at each systole of the right ventricle  $100 \times 0.988 = 98.8$  gram-meters; a gram-meter being the work done in raising one gram to the height of one meter. The work of both ventricles together would be  $256.7 + 98.8 = 355.5$  gram-meters. The foregoing estimates are offered not as statements of what does occur, but as very rough indications of what may occur. Even

<sup>1</sup> F. Goltz und J. Gaule: "Ueber die Druckverhältnisse im Innern des Herzens," *Archiv für die gesammte Physiologie*, 1878, xvii S. 100.

<sup>2</sup> S. de Jager: "Ueber die Saugkraft des Herzens," *Pflüger's Archiv für die gesammte Physiologie*, 1883, S. 504, 505.

<sup>3</sup> Goltz und Gaule, *op. cit.*, S. 106.



thus, however, they are of moment. When we think of the vast number of beats executed by the heart every day, the great amount of energy rendered manifest in maintaining the circulation becomes apparent, and our interest is heightened in the fact that all of this large sum of energy is liberated in the muscular tissue of the heart itself. Thus, too, the physiological significance of the diastole is accentuated as a time of rest for the cardiac muscle, as well as a necessary pause for the admission of blood into the ventricle. To disregard minor considerations, the work done at a systole will evidently depend upon the amount of the pulse-volume, of the arterial pressure overcome, and of the velocity imparted to the ejected blood. All these are variable. The work of the ventricles therefore is eminently variable.

**The Heart's Contraction as a Source of Heat.**—In dealing with the movement of the blood in the vessels we have seen that the energy of visible motion liberated by the cardiac contractions is progressively changed into heat by the friction encountered by the blood; and that this change is nearly complete by the time the blood has returned to the heart, the kinetic energy of each systole sufficing to drive the blood from the heart back to the heart again, but probably not being much more than is required for this purpose. Practically, therefore, all the energy of the heart's contraction becomes heat within the body itself, and leaves the body under this form. As the heart liberates during every day an amount of energy which is always large but very variable, its contractions evidently make no mean contribution to the heat produced in the body and parted with at its surface.

#### H. THE MECHANISM OF THE VALVES OF THE HEART.

**Use and Importance of the Valves.**—The discussion just concluded shows the work of the heart to be the forcible pumping of a variable pulse-volume out of veins where the pressure is low into arteries where the pressure is high. It is owing to the valves that this is possible, and so dependent is the normal movement of the blood upon the valves at the four ventricular apertures that the crippling of a single valve by disease may suffice to destroy life after a longer or shorter period of impaired circulation.

**The Auriculo-ventricular Valves.**—The working of the auriculo-ventricular valves (see Fig. 18) is not hard to grasp. When the pressure within the ventricle in its diastole is low, the curtains hang free in the ventricle, although probably never in close contact with its wall. As the blood pours into the ventricle, the pressure within it rises, currents flow into the space between the wall and the valve, and probably bring near together the edges of the curtains and also their surfaces for some distance from the edges. Thus, upon the cessation of the auricular systole, the supervening of a superior pressure within the ventricle probably applies the already approximated edges and surfaces of the curtains to one another so promptly that the commencing contraction of the ventricle is not attended by regurgitation into the auricle. The principle of closure is the same for the tricuspid valve as for the mitral. As the forces are exactly equal and opposite which press together the

opposed parts of the surfaces of the curtains, those parts undergo no strain, and hence are enabled to be exquisitely delicate and flexible and therefore easily fitted to one another. On the other hand, the parts of the valve which intervene between the surfaces of contact and the auriculo-ventricular ring are tough and much thicker, as they have to bear the brunt of the pressure within the contracting ventricle. As the systole of the ventricle increases, the auriculo-ventricular ring probably becomes smaller, and the curtains of the valve probably become somewhat fluted from base to apex, so that their line of contact is a zig-zag. At the same time their surfaces of contact may increase in extent.

**Tendinous Cords and their Uses.**—The structure so far described is wonderfully effective because it is combined with an arrangement to prevent a reversal of the valve into the auricle, which otherwise would occur at once. This arrangement consists in the disposition of the tendinous cords, which act



FIG. 18.—The left ventricle and aorta laid open, to show the mitral and aortic semilunar valves (Henic).

as guy-ropes stretched between the muscular wall of the ventricle and the valve, whether mitral or tricuspid. These cords are tough and inelastic, and, like the valve, are coated with the slippery lining of the heart. They are stout where they spring from the ansele, but divide and subdivide into branches, strong but sometimes very fine, which proceed fan-wise from their



stem to their insertions (see Fig. 18). These insertions are both into the free margin of the valve and into the whole extent of that surface of it which looks toward the wall of the ventricle, quite up to the ring. By means of this arrangement of the cords each curtain is held taut from base to apex throughout the systole of the ventricles, the opposed surfaces being kept in apposition, and the parts of the curtains between these surfaces and the ring being kept from bellying unduly toward the auricle. Each curtain is held sufficiently taut from side to side as well, because the tendinous cords inserted into one lateral half of the curtain spring from a widely different part of the wall of the heart from those of the other lateral half of it (see Fig. 18). At all times, therefore, even when the walls of the ventricle are most closely approximated during systole, the cords may pull in slightly divergent directions upon the two lateral halves of each curtain. This arrangement of the cords may also cause them, when taut, to pull in slightly convergent directions upon the contiguous lateral halves of two neighboring curtains and thus to favor the pressing of them together (see Fig. 18).

**Papillary Muscles and their Uses.**—In the left ventricle the tendinous cords arise in two groups, like bouquets, from two test-like muscular projections which spring from opposite points of the wall of the heart, and which are called the "papillary muscles" (see Fig. 18). One of these gives origin to the cords for the right half of the anterior and for the right half of the posterior curtain; the other papillary muscle gives rise to the cords for the left halves of the two curtains. Each papillary muscle is commonly more or less subdivided (see Fig. 18). The same principles are carried out, but less regularly, for the origins of the tendinous cords of the more complex tricuspid valve. Various opinions have been held as to the use of the papillary muscles. It seems probable that during the change of size and form wrought in the ventricle by its systole, the origins of the tendinous cords and the auriculo-ventricular ring tend to be approximated and the cords to be slackened in consequence. Perhaps this is checked by a compensatory shortening of the papillary muscles, due to their sharing in the systolic contraction of the muscular mass of which they form a part. Observations have been made which have been interpreted to mean that the papillary muscles begin their contraction slightly later and end it slightly earlier than the mass of the ventricle.<sup>1</sup>

**Semilunar Valves.**—The anatomy and the working of the semilunar valves are the same in the aorta as in the pulmonary artery, and one account will answer for both valves. Each valve is composed of three entirely separate segments, set end to end within and around the artery just at its origin from the ventricle. The attachments of the segments occupy the entire circumference of the vessel (Fig. 18). Like the tricuspid and mitral valves, each semilunar segment is composed of a sheet of tissue which is tough, thin, supple, and slippery; but the semilunar valves differ from the tricuspid and

<sup>1</sup>C. S. Roy and J. G. Adami: "Heart-beat and Pulse-wave," *The Practitioner*, 1890, i. p. 88.



mitral, not only in the complete distinctness of their segments, but also in their mechanism. The tendinous cords are wholly lacking, and each segment depends upon its direct connection with the arterial wall to prevent reversal into the ventricle during the diastole of the latter. If the artery be carefully laid open by cutting exactly between two of the segments, each of the three is seen to have the form of a pocket with its opening turned away from the heart (see Fig. 18). Behind each segment, the artery is dilated into one of the hollows or "sinuses" of Valsalva.<sup>1</sup> As the valve lies immediately above the base of the ventricle the segments rest upon the top of the thick muscular wall of the latter, which affords them a powerful support (see Fig. 19). Each segment is attached by the whole length of its longer edge to the artery, while the free margin is formed by the shorter edge. It is this arrangement which renders reversal of a segment impossible (see Fig. 18).

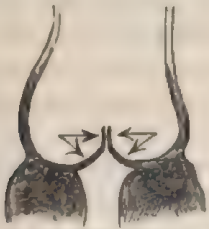


FIG. 19.—Diagram to illustrate the mechanism of the semilunar valve.



FIG. 20.—Diagram to illustrate the mechanism of the semilunar valve and corpora Arantii.

While the blood is streaming from the ventricle into the artery, the three segments are pressed away by the stream from the centre of the vessel, but never nearly so far as to touch its wall. At all times, therefore, a pouch exists behind each segment, which pouch freely communicates with the general cavity of the artery. As the ventricular systole nears its end, the ventricular cavity doubtless becomes narrowed just below the root of the artery, and with it the arterial aperture itself, while currents enter the sinuses of Valsalva. Thus for a double reason the three segments of the valve are approximated, and probably the last blood pressed out of the ventricle issues through a narrow chink between them. The instant that the pressure in the ventricle falls below the arterial pressure, the three segments must be brought together by the superior pressure within the artery, and tightly closed by its forcible recoil, without regurgitation having occurred in the process (see Figs. 19, 20).<sup>2</sup>

**Lunulæ and their Uses.**—Each segment of a semilunar valve, when closed, is in firm contact with its fellows not only at its free margin but also over a considerable surface, marked in the anatomy of the segment by the two "lunulæ" or little crescents, each of which occupies the surface of the segment from one of its ends to the middle of its free margin, the shorter edge

<sup>1</sup> Named from the Italian physician and anatomist Valsalva of Bologna, born in 1666.

<sup>2</sup> L. Krehl: "Beiträge zur Kenntnis der Füllung und Entleerung des Herzens," *Abhandlungen der math.-physischen Classe der k. bayerischen Gesellschaft der Wissenschaften*, 1891, Bd. xvii. No. 5, S. 380.

of the lunula being one-half of the free margin of the segment (see Fig. 18). Over the surface of each lunula each segment is in contact with a different one of its two fellows (see Fig. 20). The firmness of closure thus secured is shown by Figure 19, which represents a longitudinal section of the artery, passing through two of the closed segments. The forces which press together the opposed surfaces are equal and opposite, and the parts of the segments which correspond to these surfaces undergo no strain. The lunulæ, therefore, like the mutually opposed portions of the mitral or tricuspid valve, are very delicate and flexible, while the rest of each semilunar segment is strongly made, to resist of itself the arterial pressure.

**Corpora Arantii and their Uses.**—At the centre of the free margin of each semilunar segment, just between the ends of the two lunulæ, there is a small thickening, more pronounced in the aorta than in the pulmonary artery, called the “body of Aranzi”<sup>1</sup> (*corpus Arantii*). This thickening both rises above the edge and projects from the surface between the lunulæ. When the valve is closed, the three corpora Arantii come together and exactly fill a small triangular chink, which otherwise might be left open just in the centre of the cross section of the artery (see Figs. 18, 20).

The foregoing shows that the mechanism of the semilunar valves is no less effective, though far simpler, than that of the mitral and tricuspid. That the latter two should be more complex is natural; for each of them must give free entrance to and prevent regurgitation from a chamber which nearly empties itself, and hence undergoes a very great relative change of volume; while the arterial system is at all times distended and undergoes a change of capacity which is relatively small while receiving a pulse-volume and transmitting it to the capillaries.

#### I. THE CHANGES IN FORM AND POSITION OF THE BEATING HEART, AND THE CARDIAC IMPULSE.

**General Changes in the Heart and Arteries.**—During the brief systole of the auricles these diminish in size while the swelling of the ventricles is completed. During the more protracted systole of the ventricles, which immediately follows, these diminish in size while the auricles are swelling and the injected arteries expand and lengthen. During the greater part of the succeeding diastole of the ventricles both these and the auricles are swelling, and all the muscular fibres of the heart are flaccid, up to the moment when a new auricular systole completes the diastolic distention of the ventricles, as above stated. During the ventricular diastole, as the great arteries recoil they shrink and shorten. The changes of size in the beating heart depend entirely upon the changes in the volume of blood contained in it, and not upon changes in the volume of the muscular walls. The muscular fibres of the heart agree with those found elsewhere in not changing their volume appreciably during contraction, but their form only. The cardiac cycle thus runs its course with

<sup>1</sup> Named from Julius Cesar Aranzi of Bologna, an Italian physician and anatomist, born in 1530.



regularly recurring changes of size in the auricles, the ventricles, and the arteries. These changes of size are accompanied by corresponding changes in the form and position of the heart, which are both interesting in themselves and important in relation to the diagnosis of disease. The basis of their study consists in opening the chest and pericardium of an animal, and seeing, touching, and otherwise investigating the beating heart. The changes in the beating heart, moreover, underlie the production of the so-called cardiac impulse, or apex-beat, which is of interest in physical diagnosis.

**Observation of the Heart and Vessels in the Open Chest.**—The beating heart may be exposed for observation in a mammal by laying it upon its back, performing tracheotomy, and completely dividing the sternum in the median line, beginning at the ensiform cartilage. Artificial respiration is next established, a tube having been tied into the trachea before the chest was opened. The two sides of the chest are now drawn asunder and the pericardium is laid open to expose the heart.

If, in any mammal, the ventricles be lightly taken between the thumb and forefinger, the moment of their systole is revealed by the sudden hardening of the heart produced by it, as the muscular fibres contract and press with force upon the liquid within. On the other hand, the ventricular diastole is marked by such flaccidity of the muscular fibres that very light pressure indents the surface, and causes the finger to sink into it, in spite of care being taken to prevent this. Commonly, therefore, at the systole the thumb and finger are palpably and visibly forced apart, no matter where applied, in spite of the fact that the volume of the ventricles is diminishing. This sinking of the finger or of an instrument into the relaxed wall of the heart has given rise to many errors of observation regarding changes during the beat. The time when the ventricles are hardened beneath the finger coincides with the up-stroke of the arterial pulse near the heart, and, as shown by Harvey,<sup>1</sup> with the time when an intermittent jet of blood springs from a wound of either ventricle. The hardening is proven thus to mark the systole of the ventricles. Those changes of size, form, and position of the exposed heart which accompany the hardening of the ventricles beneath the finger are therefore the changes of the ventricular systole; and the converse changes are those of the ventricular diastole. To interpret all the changes correctly by the eye alone, without the aid of the finger or of the jet of blood, is a task of surpassing difficulty in a rapidly beating heart, as was eloquently set forth by Harvey.<sup>2</sup>

**Changes of Size and Form in the Beating Ventricles.**—In a mammal, lying upon its back, with the heart exposed, the ventricles evidently become smaller during their systole. Their girth is everywhere diminished and their length also, the latter much less than the former; indeed the diminution in length is a disputed point. Not merely a change of size, but a

<sup>1</sup> *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, 1628, p. 23; Willis' translation, Bowie's edition, 1889, p. 23.

<sup>2</sup> *Op. cit.*, 1628, p. 20; Willis' translation, Bowie's edition, p. 20.



change of form is thus produced ; the heart becomes a smaller and shorter, but a more pointed cone. The narrowing from side to side is very conspicuous. In the opened chest of a mammal lying on its back this narrowing is accompanied by a change which probably does not occur in the unopened chest, viz., by some increase in the diameter of the heart from breast to back, so that the surface of the ventricles toward the observer becomes more convex (see p. 116). Thus the base of the ventricles, which tended to be roughly elliptical during their relaxation, tends to become circular during their contraction ; and the diameter of the circle is greater than the shortest diameter of the ellipse, which latter diameter extends from breast to back. At the same time, the area of the base when circular and contracted is much less than when elliptical and relaxed.<sup>1</sup> Naturally, none of these comparisons to mathematical figures makes any pretence to exactness. At the same time that the contracting heart undergoes these changes, the direction of its long axis becomes altered. In animals in which the heart is oblique within the chest, the line from the centre of the base to the apex, that is, the long axis, while it points in general from head to tail, points also toward the breast and to the left. In an animal lying on its back, the ventricles when relaxed in diastole tend to form an oblique cone, the apex having subsided obliquely to the left and toward the tail. As the ventricles harden in their systole, they tend to change from an oblique cone to a right cone ; the long axis tends to lie more nearly at right angles to the base ; and consequently the apex, unfettered by pericardium or chest-wall, makes a slight sweep obliquely toward the head and to the right, and thus rises up bodily for a little way toward the observer. This movement was graphically called by Harvey the erection of the heart.<sup>2</sup> It is accompanied by a slight twisting of the ventricles about their long axis, in such fashion that the left ventricle turns a little toward the breast, the right ventricle toward the back.

**Changes of Position in the Beating Ventricles.**—The changes in form imply changes in position. The oblique movement of the long axis implies that in systole the mass of the ventricles sweeps over a little toward the median line and also a little toward the head. The shortening of the long axis implies that either the apex recedes from the breast, or the base of the ventricles recedes from the back, or both. Of these last three possible cases, the second is the one that occurs. The oblique movement of the apex is accompanied by no recession of it ; but the auriculo-ventricular furrow and the roots of the aorta and pulmonary artery move away from the spinal column as the injected arteries lengthen and expand, and, as the auricles swell, during the contraction of the ventricles. During their diastole the ventricles are soft ; they swell ; and changes of form and position occur which are simply converse to those of the systole and have been indicated already in dealing with the latter.

<sup>1</sup> C. Ludwig: "Ueber den Bau und die Bewegungen der Herzventrikel," *Zeitschrift für rationelle Medizin*, 1849, vii. S. 189.

<sup>2</sup> *Op. cit.*, 1628, p. 22. Translation, 1889, p. 22.

**Changes in the Beating Auricles.**—Except in small animals, the walls of both the ventricles are so thick that the color of the two is the same and is unchanging, namely, that of their muscular mass; but the walls of the auricles are so thin that their color is affected by that of the blood within, so that the right auricle looks bluish and dark and the left auricle red and bright. During the brief systole of the auricles they are seen to become smaller and paler as blood is expelled from them, while their serrated edges and auricular appendages shrink rapidly away from the observer. The changes of the auricular systole are seen to precede immediately the changes of the systole of the ventricles and to succeed the repose of the whole heart. During the relatively long diastole of the auricles these are seen to swell, whether the ventricles are shrinking in systole or are swelling during the first and greater part of their diastole.

**Changes in the Great Veins.**—In the venæ cavæ and pulmonary veins a pulse is visible, more plainly in the former than in the latter, which pulse has the same rhythm as that of the heart's beat. The causes of this pulse are complex. It depends in part upon the rhythmic contraction of muscular fibres in the walls of the veins near the auricles, which must heighten the flow into the latter, and which contraction the auricular systole immediately follows.<sup>1</sup> This venous pulse will be mentioned again in discussing the details of the events of the cycle (see p. 138).

**Changes in the Great Arteries.**—It is interesting to note that even in so large an animal as the calf the pulse of the aorta or of the pulmonary artery can hardly be appreciated by the eye, so far as the increase in girth of either vessel is concerned. The expansion of the artery affects equally all points in its circumference, and being thus distributed, is so slight in proportion to the girth of the vessel that the profile of the latter scarcely seems to change its place. The lengthening of the expanding artery can be more readily seen.

**Effects of Opening the Chest.**—Such are the changes observed in the heart and vessels when exposed in the opened chest of a mammal lying on its back. The question at once arises, Can these changes be accepted as identical with those which occur in the unopened chest of a quadruped standing upon its feet, or of a man standing erect? It will be most profitable to deal at once with the case of the human subject. What are the possible, indeed probable, differences between the changes in the heart in the unopened upright chest and in the same when opened and supine?

When air is freely admitted to both pleural sacs, all those complex effects upon the circulation are at once abolished which we have seen to be caused by the elasticity of the lungs and the movements of respiration. The artificial respiration will have an effect upon the pulmonary transit of the blood and so upon the circulation; but the details of this effect are not the same as those of natural respiration, and, for our present purpose, may be disregarded.

<sup>1</sup> T. Lauder Brunton and F. Fayrer: "Note on Independent Pulsation of the Pulmonary Veins and Vena Cava," *Proceedings of the Royal Society*, 1876, vol. xiv. p. 174.



What has been abolished is the continual suction, rhythmically increased in inspiration, exerted by the lungs upon the heart and all the vessels within the chest, which suction at all times favors the expansion and resists the contraction of the cavities of the heart and of the vessels. On the opening of both pleural sacs the heart and vessels are exposed to the undiminished and unvarying pressure of the atmosphere. Moreover, the heart has ceased to be packed, as it were, between the pleurae and lungs to right and left, the spine, the front of the chest-wall, and the diaphragm. From these considerations it follows that the heart must be freer to change its form and position in the opened than in the unopened chest; and that these changes must be more modified by simple gravity in the former case than in the latter. Even in the open chest we have studied these changes only in an animal lying on its back. But if we turn the creature to either side, or place it upright in imitation of the natural human posture, the ventricles of the exposed heart in any case tend to assume, in systole, the same form, which has been compared roughly to a right cone with a circular base. This is the form proper to the hardened structure of branching and connected fibres of which the contracting ventricles consist. But if the exposed ventricles be noted in diastole, it will appear that their form depends very largely upon the effects of gravity upon the exceedingly soft and yielding mass formed by their relaxed fibres. We have seen them, in diastole, to flatten from breast to back, to spread out from side to side, to gravitate toward the tail and to the left. If the animal is laid on its side, they flatten from side to side, they spread out from breast to back, and gravitate to the right or left, as the case may be.<sup>1</sup>

**Probable Changes in the Heart's Form and Position in the Unopened Chest.**—It is fair to conjecture that the increase of the relaxed ventricles in girth and in length which is seen in the open chest would not be greatly different in the closed chest of a man in the upright posture. But it is probable that the flattening of the exposed heart from breast to back, which is seen in diastole, would not occur if the chest were closed. It is precisely in this direction that the flaccid heart exposed in the supine chest would be flattened unduly by its own weight, when deprived of many of its anatomical supports and of the dilating influence of the lungs. The flattening from breast to back must cause an exaggerated spreading out from side to side and hence an unduly elliptical form of the base, inasmuch as, at the same time, the girth of the ventricles is increasing as they enlarge in their diastole. Conversely, it is probable, both *a priori* and from experimental evidence, that in the chest, when closed and upright, the diminution in size of the contracting ventricles proceeds more symmetrically; that their girth everywhere diminishes through a diminution of the diameter from breast to back as well as of that from side to

<sup>1</sup> J. B. Haycraft: "The Movements of the Heart within the Chest cavity, and the Cardiogram," *The Journal of Physiology*, vol. xii., Nos. 5 and 6, December, 1891, p. 448; J. B. Haycraft and D. R. Paterson: "The Changes in Shape and in Position of the Heart during the Cardiac Cycle," *The Journal of Physiology*, vol. xix., Nos. 5 and 6, May, 1896, p. 496.



side, and not through an exaggerated lessening of the latter and an actual increase of the former. In this case, too, the base would tend to become more circular during the systole by means of a less marked change from the diastolic form.<sup>1</sup>

It has been said that in systole the ventricles are somewhat shortened in the exposed heart, and probably also in the unopened human chest. In the open chest the apex does not recede at all in virtue of this shortening; on the contrary, the base of the ventricles is seen to move toward the apex, and away, therefore, from the spine. Experiment has proven that the foregoing is true also of the unopened chest.<sup>2</sup> It has been noted already that this movement of the base, which in the upright chest would be a descent, is accompanied by a lengthening of the aorta and pulmonary artery as their distention takes place. Very probably it is the thrust of the lengthened arteries which largely causes the descent of the base of the contracting ventricles, which descent compensates for the shortening of the ventricles and retains the apex in contact with the chest-wall.

**The Impulse or Apex-beat.**—It must always have been a matter of common knowledge that, in man, a portion of the heart lies so close to the chest-wall that, at each beat, the soft parts of that wall may be seen and felt to pulsate over a limited area. This is commonly in the fourth or fifth intercostal space, midway between the left margin of the sternum and a vertical line let fall from the left nipple. A similar pulsation may be observed in other mammals. The protrusion of the chest-wall at the site of this "impulse" or "apex-beat" occurs when the arteries expand, and the up-stroke of their pulse is felt; and the recession of the chest coincides with the shrinking of the arteries away from the finger. The impulse proper, that is the protrusion of the chest-wall, occurs, therefore, at the time of the systole of the ventricles. By far the most important factor of the apex-beat is probably the effort of the hardening ventricles to change the direction of their long axis against the resistance of the chest-wall. A heart severed from the body and bloodless, if laid upon a table, lifts its apex as it hardens in systole and assumes its proper form. If a finger be placed near enough to the rising apex to be struck by it, the same sensation is received as from the impulse.

It is interesting to note that around the point where the soft parts of the chest are protruded by the impulse, they are found to be very slightly drawn in at the time of its occurrence. This drawing-in is called the "negative impulse," and must be caused by the diminution in size of the contracting ventricles. These are air-tight within the chest, and so their forcibly lessened surface must be followed down, in varying degrees, under the pressure of the atmosphere, by the elastic and yielding lungs and by the far less yielding soft parts of the chest-wall.

The apex-beat can be brought to bear in various ways upon a recording lever, and thus be made to inscribe upon the kymograph a rhythmically fluctuating trace, which is called a cardiogram. Considerable attention has been

<sup>1</sup> J. B. Haycraft: *loc. cit.*

<sup>2</sup> Haycraft: *loc. cit.*

given to the elucidation of the curve thus recorded; but, so far, too little agreement has been reached for the subject to be entered upon here.<sup>1</sup>

### J. THE SOUNDS OF THE HEART.

If the ear be applied to the human chest, at or near the place of the apex-beat, the heart's pulsation will be heard as well as felt. This fact was known to Harvey.<sup>2</sup> About two hundred years later than Harvey, in 1819, the French physician Laënnec, the inventor of auscultation, made known the fact that each beat of the heart is accompanied not by one but by two separate sounds. He also called attention to their great importance in the diagnosis of the diseases of the heart.<sup>3</sup>

**Relations of the Sounds.**—The first sound is heard during the time when the apex-beat is felt; it therefore coincides with the systole of the ventricles. The second sound is much shorter, and follows the first immediately, or, to speak more strictly, after a scarcely appreciable interval. The second sound, therefore, coincides with the earlier part of the diastole of the ventricles. The second sound is followed in its turn by a period of silence, commonly longer considerably than the second sound, which silence lasts till the beginning of the first sound of the next ventricular beat. The period of silence, therefore, coincides with the later, and usually longer, portion of the diastole of the ventricles, and with the systole of the auricles. It is interesting that the great auscultator, Laënnec, offered no explanation of the cause of either sound, while he made and reiterated the incorrect and misleading statement that the second sound coincides with the systole of the auricles. When the heart beats oftener than usual, each beat must be accomplished in a shorter time; and it is found that, during a briefer beat, the period of silence is shortened much more than the period during which the two sounds are audible; which latter period may not be altered appreciably.

**Characters of the Sounds.**—The first sound is not only comparatively long, but is low-pitched and muffled. The second sound is comparatively short, and is high and clear. The two sounds, therefore, are sharply contrasted in duration, pitch, and quality. A rough notion of the contrasted characters of the sounds may be obtained by pronouncing the meaningless syllables "lubb dup." In other mammals the sounds have substantially the same characters as in man.

**Cause of the Second Sound.**—Since Laënnec's time, the cause of the second sound has been demonstrated by experiment. The second sound is due to the vibrations caused by the simultaneous closure of the semilunar valves of the pulmonary artery and of the aorta, when the diastole of the ventricles has just begun. This cause was first suggested by the French physician

<sup>1</sup> M. von Frey: *Die Untersuchung des Pulses*, etc., 1892, S. 102; R. Tigerstedt: *Lehrbuch der Physiologie des Kreislaufes*, Leipzig, 1893, S. 112.

<sup>2</sup> *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, 1628, p. 30; Willis's translation, Bowie's edition, 1889, p. 34.

<sup>3</sup> R. T. H. Laënnec: *De l'auscultation médiate*, etc., Paris, 1819.



Rouanet in 1832;<sup>1</sup> not long afterward it was conclusively proven by experiment by the English physician C. J. B. Williams.<sup>2</sup>

Dr. Williams's experiment was as follows: In a young ass the chest was opened and the heart was exposed. It was ascertained that the second sound was audible through a stethoscope applied to the heart itself. A sharp hook was then passed through the wall of the pulmonary artery, and was so directed as to make the semilunar valve incompetent temporarily. By means of a second hook, the aortic semilunar valve was likewise made incompetent. When both hooks were in position, the heart was auscultated afresh, and the second sound was found to have disappeared, and to be replaced by a hissing murmur. The hooks were withdrawn during auscultation, and at the moment of withdrawal the murmur disappeared and the normal second sound recurred. Subsequent clinical and post-mortem observations have shown that the second sound may be altered by disease which cripples the aortic valves.

**Causes of the First Sound.**—The causes of the first sound have not been proven so clearly by the available evidence, which is partly experimental and partly derived from physical diagnosis followed by post-mortem verification. The first sound, like the second, was ascribed by Rouanet<sup>3</sup> to vibrations depending upon valvular closure,—the simultaneous closure of the tricuspid and mitral valves; but the persistence of the sound throughout the whole ventricular systole made this cause less probable than in the case of the second sound. Williams,<sup>4</sup> on the other hand, ascribed the first sound to the contraction of the muscular tissue of the ventricles,—an explanation consistent with the muffled quality of the first sound, and with its persistence throughout the systole of the ventricles. It is now believed by many that both of the foregoing explanations are correct, and that the first sound is composite in its origin, and due both to closure of the valves and to muscular contraction. The evidence in favor of these causes is, briefly, as follows:

In favor of a valvular element in the first sound, it is maintained: That if the ventricles of a dead heart be suddenly distended with liquid, the mitral and tricuspid valves produce a sound in closing; and that clinical and post-mortem observations show that the first sound may be altered by disease which cripples the auriculo-ventricular valves.

In favor of an element in the first sound caused by muscular contraction it is maintained: That in a still living but excised heart, the first sound continues to be heard under circumstances which preclude the closure and vibration of the valves, and leave in operation no conceivable cause for the first sound except muscular contraction. Experiments upon the first sound of the excised heart were reported in 1868 by Ludwig and Dogiel,<sup>5</sup> and were

<sup>1</sup> J. Rouanet: *Analyse des bruits du cœur*, Paris, 1832.

<sup>2</sup> C. J. B. Williams: *Die Pathologie und Diagnose der Krankheiten der Brust, etc.* Nach der dritten, sehr vermehrten Auflage aus dem Englischen übersetzt, Bonn, 1838. (The writer has not seen an English edition.)

<sup>4</sup> *Loc. cit.*

<sup>5</sup> *Loc. cit.*

<sup>5</sup> J. Dogiel und C. Ludwig: "Ein neuer Versuch über den ersten Herzton," *Berichte über die Verhandlungen der k. sächsischen Gesellschaft der Wissenschaften zu Leipzig, math.-physische Classe*, 1868, S. 89.



performed upon the dog as follows: The heart was exposed during artificial respiration, and loose ligatures were placed upon the vena cava, the pulmonary artery, the pulmonary veins, and the aorta. Next, the loose ligatures were tightened in the order above written, during which process the beating heart necessarily pumped itself as free as possible of blood. The vessels were then divided distally to the ligatures, and the heart was excised and suspended in a conical glass vessel containing freshly drawn defibrinated blood, in which the heart was fully immersed without touching the glass at any point. Under these conditions the excised heart might execute as many as thirty beats. The conical glass vessel was supported in a "ring-stand." The narrow bottom of the vessel consisted of a thin sheet of india-rubber, with which last was connected the flexible tube and ear-piece of a stethoscope. By means of the latter any sound produced by the beating heart could be heard through the blood and the sheet of rubber. The second sound was not heard; but at each contraction of the ventricles the first sound was heard, not of the same length or loudness as normally, but otherwise unaltered. The conditions of experiment were held to preclude error resulting from adventitious sounds; moreover, the heart before excision had pumped itself free from all but a fraction of the amount of blood required to close the valves, and had been so treated that no more could enter. It was therefore believed to be practically impossible that the sound heard could have its origin at the valves; and no origin remained conceivable other than in the muscular contraction of the ventricular systole. Later experiments, in which the auriculo-ventricular valves have been rendered incompetent by mechanical means, have seemed to confirm the importance of muscular contraction as a cause of the first sound.<sup>1</sup>

By the use of a stethoscope combined with a peculiar resonator, the German physician Wintrich of Erlangen<sup>2</sup> satisfied himself that he could analyze the first sound upon auscultation, so as to detect in it two components, one higher pitched, which he attributed to the vibration of the auriculo-ventricular valves, and a component of lower pitch, attributed to the muscular contraction of the heart. The other experiments above referred to, however, which sustain muscular contraction as a cause of the first sound, did not reveal a change of pitch following incompetence of the valves, but only a diminution in loudness and duration.

Both the closure of the cuspid valves and the contraction of the muscular tissue of the ventricles are rejected by a recent observer as causes of the first sound, which he ascribes to the opening of the semilunar valves.<sup>3</sup>

<sup>1</sup> L. Krehl: "Ueber den Herzmuskelton," *Archiv für Anatomie und Physiologie, Physiologische Abtheilung*, 1889, S. 253; A. Kasem-Bek: "Ueber die Entstehung des ersten Herztones," *Pflüger's Archiv für die gesammte Physiologie*, 1890, Bd. xlvii. S. 53.

<sup>2</sup> Wintrich: "Experimentalstudien über Resonanzbewegungen der Membranen," *Sitzungsberichte der phys.-med. Societät zu Erlangen*, 1873; Wintrich: "Ueber Causation und Analyse der Herztöne," *Ibid.*, 1875.

<sup>3</sup> R. Quain: "On the Mechanism by which the First Sound of the Heart is Produced," *Proceedings of the Royal Society*, vol. lxi. p. 331.

**K. THE FREQUENCY OF THE CARDIAC CYCLES.<sup>1</sup>**

In a healthy full-grown man, resting quietly in the sitting posture, the heart beats on the average about 72 times a minute. In the full-grown woman the average is slightly higher, perhaps 80 to the minute. The heart beats less frequently in tall people than in short ones. The difference between men and women largely depends upon this, but careful observation shows that in the case of men and women of the same stature the heart-beats are slightly more frequent in the women. There is, therefore, a real difference as to the pulse between the sexes. Shortly before and after birth the heart-beats are very frequent, from 120 to 140 to the minute. During childhood and youth, the frequency diminishes gradually, the average falling below 100 to the minute at about the sixth year, and below 80 to the minute at about the eighteenth year. In extreme old age the pulse becomes slightly increased in frequency. It must, however, be borne in mind that there are very wide differences between individuals as to the average frequency of the heart-beats. Pulses of 40 and even fewer strokes to the minute, or, on the other hand, of more than 100 to the minute, are natural to some healthy people.

In every individual the frequency of the pulse varies decidedly, and may vary very greatly, during each twenty-four hours. It is least during sleep, and less in the lying than in the sitting posture. Standing makes the heart beat oftener, the difference being greater between standing and sitting than between sitting and lying. During muscular exercise the pulse-rate is much increased, violent exercise carrying it possibly to 150 or even more. Thermal influences have a marked effect, a hot bath, for instance, heightening the frequency of the pulse and a cold bath diminishing it. The taking of a meal also commonly puts up the frequency. The influence of emotion upon the heart's contractions is well known. It may act either to heighten the rate or to lower it. Finally, the practising physician soon learns that the heart's rate is more easily affected by comparatively slight causes, emotional or otherwise, in women, and especially in children, than in men—a fact of some importance in diagnosis.

The causes of the differences referred to in this section are partly unknown, and partly belong to the subject of the regulation of the circulation.

**L. THE RELATIONS IN TIME OF THE MAIN EVENTS OF THE CARDIAC CYCLE.**

We have now considered the effects produced by the cardiac pump; its general mode of working; and the actual frequency of its strokes. We must next study certain important details relating to the individual strokes or beats of the ventricles and of the auricles. For this study the basis has already been laid in the sections headed "Causes of the Blood-flow" (p. 77), "Mode of Working of the Pumping Mechanism" (p. 78), "The Cardiac Cycle" (p. 104), and "Use and Importance of the Valves" (p. 108). These sections

<sup>1</sup> Tigerstedt: *Lehrbuch der Physiologie des Kreislaufes*, Leipzig, 1893, S. 27-35; Vierordt: *Daten und Tabellen zum Gebrauche für Mediciner*, 1888, S. 105-109, 259.



should now be read again in the order just given. Details can best be dealt with if we use, instead of the more familiar word "beat," the more technical one "cycle."

**The Auricular Cycle; the Ventricular Cycle; the Cardiac Cycle.**—Each systole and succeeding diastole of the auricles constitute a regularly recurring pair of events which may truly be spoken of as an "auricular cycle;" and so also it is exact to say that the ventricles have their cycle, consisting of systole and succeeding diastole. As soon, however, as we strive for clearness, we find that the useful phrase "cardiac cycle" is necessarily arbitrary and imperfect. A perusal of the account given on p. 78 of the "Mode of Working of the Pumping Mechanism" shows at once that each auricular cycle, consisting of systole followed by diastole, must begin shortly before the corresponding ventricular cycle begins, and must end shortly before the corresponding ventricular cycle ends. The pumping mechanism is such that the auricular systole is completed just before the ventricular systole begins. The phrase "cardiac cycle" implies a reference to both auricular and ventricular events; if now we assume that the beginning of the auricular systole marks the beginning of the cardiac cycle, this must end either with the end of the auricular diastole or with the end of the ventricular diastole. In the former case the cardiac cycle would coincide with the auricular cycle, but would begin before the end of one ventricular diastole and would end before the end of another, thus containing no one complete ventricular diastole. In the second case, the cardiac cycle would contain one complete ventricular diastole and a fraction of another, and would also contain two auricular systoles. The second case is clearly even more objectionable than the first. The cardiac cycle had best be defined as consisting of all the events both auricular and ventricular which occur during one complete auricular cycle. The above discussion deals with a phrase which is a constant stumbling-block to students; and the question may well be asked, Why should the expression "cardiac cycle" not be abolished? The answer is, that this phrase is indispensable in order to accentuate certain important relations of the auricular cycle to the ventricular. During a heart-beat there is a period when the auricles and ventricles are in diastole at the same time. During this period, as we have seen, blood is passing from the veins directly through the auricles into the ventricles, and all the muscular fibres of the heart are resting. This period is therefore called that of "the repose of the whole heart," or the "pause." Whenever the heart is not wholly at rest, either auricles or ventricles must be in systole. We see, therefore, that each cardiac cycle must coincide with an auricular systole, the instantly succeeding ventricular systole, and a period of repose of the whole heart; and it is precisely these two systoles and the succeeding universal rest which most engage the attention when the beating heart is looked at in the opened chest. These three phenomena, it will be noted, exactly coincide with one complete auricular cycle, and so do not confuse the definition of the cardiac cycle which has been given already. We see, therefore, that the phrase which seemed at first so



misleading has a real value, and will cease to confuse if its limitations be carefully noted.

**The Brevity and Variability of Each Cycle.**—From the frequency with which the cycles recur, it follows at once that each one, with its complex changes in the walls, chambers, and valves, is very rapidly performed. If, for instance, the heart beat 72 times in one minute, each cycle occupies only a little more than 0.83 of a second. The brevity of each cycle is both an important physiological fact and a cause of difficulty in studying details. Each cycle, however, necessarily is capable of completion in much less time if the pulse-rate rise; for instance, during exercise. If repeated 144 times a minute instead of 72 times, each cycle would occupy only one-half of its previous time of completion. With a pulse of less than 60, again, each cycle would occupy over one second.

**Relative Lengths of the Ventricular Systole and Diastole.**—An important question is whether or no there is any fixed relation between the time required for a systole of the ventricles and the time required for a diastole. When the length of the cycle changes from one second to one-half a second, will the length of the systole be diminished by one-half, and that of the diastole also by one-half? Or is a nearly invariable time required for the ventricles to do their work of ejection, while the period of rest and of receiving blood can be greatly shortened, for a while at least? The answer is that, while both systole and diastole may vary in length, the length of the systole is much the less variable, while the diastole is greatly shortened or lengthened according as the heart beats often or seldom.

These facts have been ascertained as follows: A trained observer<sup>1</sup> auscultated the sounds of the human heart during a number of cycles, and, at the instant when he heard the beginning either of the first or of the second sound, made a mark upon the revolving drum of a kymograph by means of a signalling apparatus. Of course, careful account was taken of the time lost between the occurrence of a sound and the recording of it. It was found that the time between the beginning of the first and that of the second sound did not vary to the same degree as the frequency of the beats. Although the interval in question may not be an exact measure of the period of ventricular systole, it is sufficiently near it for the purposes of this observation.

A second method<sup>2</sup> depended upon the interpretation of the curve inscribed by a lever pressed upon the skin over a pulsating human artery. Such a curve exhibits two sudden changes of direction, which were taken to indicate approximately the beginning and end of the injection of blood by the ventricle, and, therefore, to afford a rough measure of the duration of its systole. While the interpretation of the curve in question is not wholly settled, it seems, neverthe-

<sup>1</sup> F. C. Donders: "De Rhythmus der Hartstooten," *Nederlandsch Archief voor Genees- en Natuurkunde*, 1865, p. 141.

<sup>2</sup> E. Thurston: "The Length of the Systole of the Heart as Estimated from Sphygmographic Tracings," *Journal of Anatomy and Physiology*, 1876, vol. x. p. 494.

less, to give a fair basis for conclusions as to the present question. The figures resulting from the second method are especially instructive. It was found that, with a pulse of 47 to the minute, the approximate length of the ventricular systole was 0.347 of a second; of the diastole, 0.930 of a second. With a pulse of 128 to the minute, while the systole was only moderately diminished, viz. to 0.256 of a second, the diastole was reduced to 0.213 of a second—an enormous decline.

These results upon the human subject have been confirmed upon animals by experiments in which were registered the movements of a lever laid across the exposed heart;<sup>1</sup> or the fluctuations of the pressures within the ventricles.<sup>2</sup>

By whatever means investigated, the ventricular systole is found to be shortened with the cycle, and to be lengthened with it; the diastole is shortened or lengthened much more, however. In fact, if the pulse become very frequent, the diastole may be so shortened that the "pause" nearly disappears, and the systole of the auricles follows speedily after the opening of the cuspid valves. This signifies that, for a time, the cardiac muscle can do with very little rest, and that effective means exist for a very rapid "charging" of the ventricular cavity when necessary. For the working period of the ventricle, however, a more uniform time is required. For the average human pulse-rate this time of work is decidedly shorter than the time of rest—viz. about 0.3 of a second for the former as against about 0.5 for the latter.

**Lengths of Auricular Events and of the Pause.**—The systole of the auricles is very brief, being commonly reckoned at about 0.1 of a second, as the result of various observations.<sup>3</sup> At the average pulse-rate, therefore, the auricular systole is only about one-third as long as the ventricular, and the length of the auricular diastole is to that of the ventricular as seven to five. Consequently, a cardiac cycle of 0.8 of a second would comprise an auricular systole of 0.1 of a second; a ventricular systole of 0.3 of a second; and a pause, or repose of the whole heart, of 0.4 of a second—one-half of the cycle.

**Practical Application.**—The observations above described upon the interval between the beginnings of the sounds have a practical bearing upon physical diagnosis; for they show how faulty are the statements often made which assign regular proportions to the lengths of the sounds and the silences of the heart. The length of the "second silence" must be very fluctuating, as it comprises the longer part of the fluctuating ventricular diastole. The length of the first sound and of the very brief first silence together must be very constant, as they nearly coincide with the ventricular systole.

<sup>1</sup> N. Baxt: "Die Verkürzung der Systolenzeit durch den Nervus accelerans cordis," *Archiv für Anatomie und Physiologie*, Physiologische Abtheilung, 1878, S. 122.

<sup>2</sup> M. von Frey und L. Krehl: "Untersuchungen über den Puls," *Archiv für Anatomie und Physiologie*, Physiologische Abtheilung, 1890, S. 31. W. T. Porter: "Researches on the Filling of the Heart," *Journal of Physiology*, 1892, vol. xiii. p. 531.

<sup>3</sup> H. Vierordt: *Daten und Tabellen zum Gebrauche für Mediciner*, 1888, S. 105



M. THE PRESSURES WITHIN THE VENTRICLES.<sup>1</sup>

We must now approach the study of further details of the working of the ventricular pumps, which details depend for their elucidation upon the measuring and recording of the pressures within the ventricles.

**Absolute Range of Pressure within the Ventricles and its Significance.**—In dealing with the work done by the contracting ventricles (p. 106) we have seen that the mercurial manometer, as used for studying the pressure within the arteries, is quite unable to follow the changes of the intra-ventricular pressure; but that, by the intercalation of a valve, this instrument can be converted into a useful "maximum manometer" for the measuring and recording of the highest pressure occurring within the ventricle during a given time—that is, during a certain number of cycles. It must now be added that by a simple change of valves this same instrument can at any moment be changed into a "minimum manometer."<sup>2</sup> We can thus, by means of the modified mercurial manometer, learn with fair correctness the extreme range of pressure within the ventricles. As instances of the extent of this range, two observations may be cited upon the left ventricle of the dog, the chest not having been opened. In one animal the maximum was found to be 234 millimeters of mercury, the maximum pressure in the aorta being 212 millimeters; and the minimum in the left ventricle was -38 millimeters—that is to say, 38 millimeters less than the pressure of the atmosphere, the minimum pressure in the aorta

<sup>1</sup> The matters connected with the ventricular pressure-curve may best be studied in the following writings, in which citations of other papers may be found. K. Hürthle, in *Pflüger's Archiv für die gesammte Physiologie*, as follows: "Zur Technik der Untersuchung des Blutdruckes," 1888, Bd. 43, S. 399. "Technische Mittheilungen," 1890, Bd. 47, S. 1. "Ueber den Ursprungsort der sekundären Wellen der Pulscurve," Bd. 47, S. 17. "Technische Mittheilungen," 1891, Bd. 49, S. 29. "Ueber den Zusammenhang zwischen Herzthätigkeit und Pulsform," Bd. 49, S. 51. "Kritik des Lufttransmissionsverfahrens," 1892, Bd. 53, S. 281. "Vergleichende Prüfung der Tonographen von Frey's und Hürthle's," 1893, Bd. 55, S. 319. J. A. Tschurowsky: "Vergleichende Bestimmung der Angaben des Quecksilber- und des Feder-Manometers in Bezug auf den mittleren Blutdruck," *Pflüger's Archiv für die gesammte Physiologie*, 1898, Bd. lxxii, S. 585. "Technische Mittheilungen," *Ibid.*, 1898, Bd. lxxii, S. 566. K. Hürthle: "Orientirungsversuche über die Wirkung des Oxyspartein auf das Herz," *Archiv für experimentelle Pathologie und Pharmacologie*, 1892, Bd. xxx, S. 141. W. T. Porter: "Researches on the Filling of the Heart," *The Journal of Physiology*, 1892, vol. xiii, p. 513. "A New Method for the Study of the Intracardiac Pressure Curve," *Journal of Experimental Medicine*, 1896, vol. i., No. 2. M. von Frey und L. Krehl: "Untersuchungen über den Puls," *Archiv für Anatomie und Physiologie*, Physiologische Abtheilung, 1890, S. 31. M. von Frey: "Die Untersuchung des Pulses," Berlin, 1892. "Das Plateau des Kammerpulses," *Archiv für Anatomie und Physiologie*, Physiologische Abtheilung, 1893, S. 1. "Die Ermittlung absoluter Werthe für die Leistung von Pulschreibern," *Archiv für Anatomie und Physiologie*, Physiologische Abtheilung, 1893, S. 17. "Zur Theorie der Lufttonographen," *Archiv für Anatomie und Physiologie*, Physiologische Abtheilung, 1893, S. 204. "Die Erwärmung der Luft in Tonographen," *Centralblatt für Physiologie* vom 30 Juni, 1891, Heft 7. O. Frank: "Ein experimentelles Hilfsmittel für eine Kritik der Kammerdruckcurven," *Zeitschrift für Biologie*, 1897, Bd. xxxv, S. 478. R. Rubbrecht: "Recherches cardiographiques chez les Oiseaux," *Archives de Biologie*, 1898, t. xv, p. 647. J. Waroux: "Du tracé myographique du cœur exsangue," *Ibid.*, 1898, t. xv, p. 661.

<sup>2</sup> F. Goltz und J. Gaule: "Ueber die Druckverhältnisse im Innern des Herzens," *Pflüger's Archiv für die gesammte Physiologie*, 1878, xvii, S. 100.



being 120 millimeters. In a second dog the figures were 176 and -30 millimeters for the ventricle, the aortic range being from 158 to 112 millimeters.<sup>1</sup> In the right ventricle of the dog such ranges as from 26 to -8 millimeters, from 72 to -25, and various intermediate values, have been noted, both in the unopened and the opened chest.<sup>2</sup> For reasons already stated (p. 103) no trustworthy figures can be given for the pressures in the pulmonary artery; but they can never fail to be less than the highest pressures within the right ventricle.

The range of pressure, therefore, within either ventricle is in sharp contrast to that within the artery which it supplies with blood; for the arterial pressure, although it fluctuates, is at all times far above that of the atmosphere, and is able, as we have seen, to maintain the circulation while the semilunar valve is closed and the ventricular muscle is at rest. On the other hand, the pressure within the ventricle, when at its highest, rises decidedly above the highest arterial pressure, and thus the ventricle can overcome this and other opposing forces, open the valve, and expel the blood. These facts have been stated already. In falling, however, the pressure within the ventricle not only sinks below that in the artery, and so permits the semilunar valve to close, but sweeps downward to a point, it may be, below the pressure of the atmosphere, and, in so doing, falls below the pressure in the auricle, and permits the opening of the auriculo-ventricular valve and the entrance of blood out of the auricle and the veins. As such a great range of pressure occurs in either ventricle of a heart which is repeating its cycles with entire regularity, it is presumable that at every cycle the pressure not only rises above that in the arteries but may sink below that of the atmosphere.

**Methods of Recording the Course of the Ventricular Pressure.**—It now becomes of interest to ascertain, if possible, not only the range, but the exact course, of these swift variations of pressure; the causes of them, and the effects which accompany them. It is hard to obtain, by the graphic method, a correct curve of the pressure within either ventricle. We have seen that the mercurial manometer is useless for this purpose; and it is very difficult to devise any self-registering manometer which shall truly keep pace with fluctuations at once so great and so rapid. The true form of this pressure-curve, therefore, still is partially in doubt, and is the subject of controversies which largely resolve themselves into contests between rival instruments. The following characters are common to the manometers with which the most serious attempts have lately been made to obtain a true and minute record of the fluctuations of pressure, even if great and rapid, within the heart or the vessels (see Fig. 21). As in the case of the mercurial manometer, a cannula, open at the end and charged with a fluid which checks the coagulation of the blood, is tied into a vessel, or, if the heart is under observation, is passed down into it through an opening in a jugular vein or a carotid artery. If the chest

<sup>1</sup> S. de Jager: "Ueber die Saugkraft des Herzens," *Pflüger's Archiv für die gesammte Physiologie*, 1883, Bd. xxxi. S. 491.

<sup>2</sup> S. de Jager: *Loc. cit.*, S. 506, 507; Goltz und Gaule: *Loc. cit.*, S. 106.

have been opened, the cannula may also be passed into the heart through a small wound in an auricle or even through the walls of the ventricle itself. The end of the cannula which remains without the animal's body is connected, air-tight, with a rigid tube of small, carefully chosen calibre, and as short as the conditions of the experiment permit. The other end of this tube is not, as in the mercurial manometer, left as an open mouth, but is connected, air-tight, with a very small metallic chamber, which constitutes, practically, a dilated blind extremity of the system formed by the tube and the cannula together. The roof of this small metallic chamber is a highly elastic disk either of thin metal or of india-rubber. Except for this small disk, all parts of the chamber, tube, and cannula are rigid. In the instruments of some observers, the entire cavity of the system formed by the chamber, tube, and cannula is filled with liquid, viz. the solution which checks coagulation. Other observers introduce this

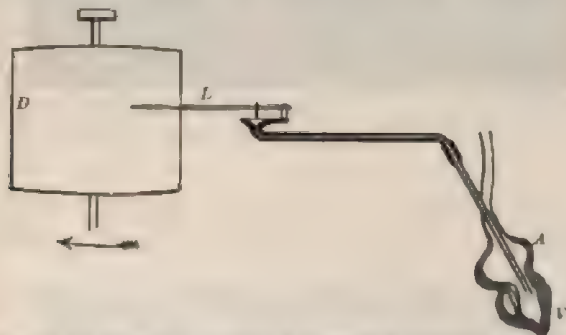


FIG. 21.—Diagram of the elastic manometer: *A*, auricle; *V*, ventricle; *D*, drum of the kymograph, revolving in the direction of the arrow, and covered with smoked paper; *L*, recording lever in contact with the revolving drum. (The working details of the instrument are suppressed for the sake of clearness.)

liquid only into the portion of the system nearest the blood; the terminal chamber, and most of the rest of the system, containing only air. In every case the blood in the vessel or in the heart is in free communication, through the mouth of the tied-in cannula, with the cavity common to the tubes and to the terminal chamber. At every rise of blood-pressure a little blood enters this cavity, room being made for it by a displacement of liquid or of air, which in turn causes a slight bulging of the elastic disk. At every fall of blood-pressure a little blood mixed with liquid leaves the tubes as the elastic disk recoils. If the disk is of the right elasticity, its rise and fall are directly proportional to the rise and fall of the blood-pressure, and can be used to measure it. With the centre of the disk is connected a delicate lever which rises and falls with the disk. The point of this lever traces upon the revolving drum of the kymograph a curve which records the fluctuations of the disk and therefore those of the blood-pressure. The elastic disk and the contents, together, of such an apparatus possess less inertia than mercury, and therefore follow far more closely rapid fluctuations of pressure. Such instruments may be called "elastic manometers," and are often called "tonographs," i. e. "tension-writers." They are of several forms.

It has been indicated already that the pressure of the blood may be communicated to the disk of an elastic manometer either by means of liquid or of air. A given series of fluctuations of blood-pressure may yield decidedly different curves according to the method of "transmission" employed to obtain them; and the controversies as to the true form of the endocardiac pressure-trace turn upon the question whether such "transmission by air" or "transmission by liquid" yield the truer curve. The objections to the former method depend upon the readier compressibility of air; the objections to transmission by liquid depend upon its greater inertia.

**The General Characters of the Ventricular Pressure-curve.**—Whatever kind of elastic manometer and of transmission be used, the curve

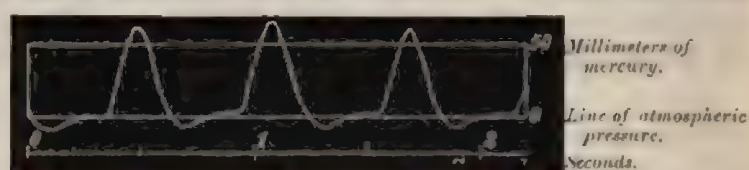


FIG. 22.—Magnified curve of the course of pressure within the right ventricle of the dog, the chest being open; to be read from left to right. Recorded by the elastic manometer, with transmission by air (von Frey).

obtained shows certain characters which are recognized by all as properly belonging to the changes of pressure within the ventricle, whether right or left. These general characters, moreover, persist after the opening of the chest. They are as follows (see Figs. 22, 23, 24): The muscular contraction of the systole begins quite suddenly, and produces a swift and ex-

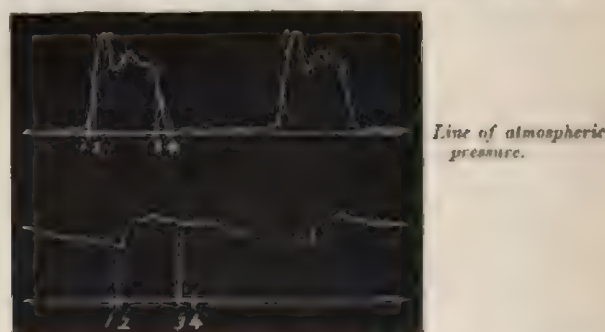


FIG. 23.—Magnified curve of the course of pressure within the left ventricle and the aorta of the dog, the chest being open; to be read from left to right. Recorded simultaneously by two elastic manometers with transmission by liquid. In both curves the ordinates having the same numbers have the following meaning: 1, the instant preceding the closing of the mitral valve; 2, the opening of the semilunar valve; 3, the beginning of the "dicrotic wave," regarded as marking the instant of closure of the semilunar valve; 4, the instant preceding the opening of the mitral valve (Porter).

tensive rise of pressure, marked in the curve by a line but slightly inclined from the vertical. In the same way the fall of pressure is nearly as sudden and as swift as the rise, and perhaps even more extensive. The systolic rise begins at a pressure a little above that of the atmosphere; the diastolic fall continues, toward its end, perhaps, with diminishing rapidity, till a point is



reached often below the pressure of the atmosphere. The pressure then rises, perhaps continuing negative for a longer or shorter time, but presently becoming equal to that of the atmosphere. Near this it continues, perhaps with a gentle upward tendency, until, near the end of the ventricular diastole, the rise becomes more rapid to the point at which the succeeding ventricular systole is to begin.

It is the course of the pressure between its rapid rise and its rapid fall which has been the most disputed. The observers who employ manometers with liquid transmission, have so far found that the high swift rise at the outset of the systole is soon succeeded by a sudden change. According to them the pressure within the manometer now exhibits fluctuations of greater or less extent which are due, partly at least, to the inertia of the transmitting liquid; but, with due allowance made for these, the cardiac pressure is seen to maintain itself at a high point throughout most of the systole until the rapid fall begins. During this period of high pressure, the height about which the fluctuations occur may remain nearly the same; or this height may gradually increase, or gradually decrease, up to the beginning of the rapid fall. As is shown by Figure 23, this course of the systolic pressure causes its curve to bend alternately downward and upward between the end of its greatest rise and the beginning of its greatest fall; but between these two points the general direction of the curve approaches the horizontal, and therefore entitles this portion of it to the name

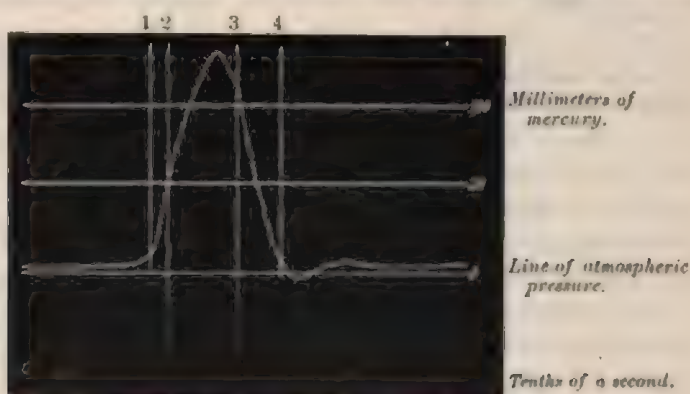


FIG. 24.—Magnified curve of the course of pressure within the left ventricle of the dog, the chest being open; to be read from left to right. Recorded by the elastic manometer with transmission by air. The ordinates have the following meaning: 1, the closure of the mitral valve; 2, the opening of the semilunar valve; 3, the closure of the semilunar valve; 4, the opening of the mitral valve (von Frey).

of the "systolic plateau," a name which becomes more truly descriptive when appropriate means are taken to eliminate the fluctuations due to inertia. The best of the manometers with air transmission yields a curve of the pressure within the ventricle which presents a different picture (Figs. 22 and 24). The steeply rising line may diminish its steepness somewhat as it ascends, but its rapid turn at the highest point of the curve is succeeded by no plateau. The line simply describes a single peak, and begins the descent which marks the rapid fall of pressure recognized by all observers. In these peaked curves

this descent is often steepest in its middle part. Such a peaked curve would indicate, of course, that there is no such thing as the maintenance, during any large part of the systole of the ventricles, of a varying but high pressure. The experienced observer who is the chief defender of the peaked curve holds the plateau to be a product either of too much friction within the manometer tubes, or of a faulty position of the cannula within the heart, whereby communication with the manometer is, for a time, cut off. The able and more numerous adherents of the plateau, on the other hand, attribute the failure to obtain it to the sluggishness of the instrument employed, or to an abnormal condition of the heart. Recent comparative tests of elastic manometers, and other studies, would seem to show that the curves obtained by liquid transmission, and which exhibit the plateau, afford a truer picture of the general course of the pressure within the ventricles than the peaked curves written by means of air.

**The Ventricular Pressure-curve and the Auricular Systole.**—It is striking testimony to the smoothness of working of the cardiac mechanism, that the curve of intra-ventricular pressure rarely gives any clear indication of the beginning or end of the auricular systole. This event may be expected to increase the pressure within the ventricles; and, in the curve, the very gentle rise which coincides with the latter and longer part of the ventricular diastole passes into the steep ascent of the commencing ventricular systole by a rounded sweep, which indicates a more rapidly heightened pressure within the ventricle during the auricular systole. As a rule, no angle reveals an instantaneous change of rate to show the beginning or end of the injection of blood by the contracting auricle (see Figs. 22, 23, 24). Occasionally, however, a slight "presystolic" fluctuation of the curve may seem to mark the auricular systole.<sup>1</sup>

**The Ventricular Pressure-curve and the Valve-play.**—It is also exceedingly striking that no curve, whether it be pointed or show the systolic plateau, gives a clear indication of the instant of the closing or opening of either valve, auriculo-ventricular or arterial (see Figs. 22, 23, 24). These instants, so important for the significance of the curve, can, however, be marked upon it after they have been ascertained indirectly. A method of general application would be as follows: Two elastic manometers are "absolutely graduated" by causing each of them to record a series of pressures already measured by a mercurial manometer. The two elastic manometers can then be made to mark upon the same revolving drum the simultaneous changes of pressure in a ventricle and in its auricle, or in a ventricle and its artery. The pressure indicated by any point of either curve can then be calculated in terms of millimeters of mercury. That point upon the intra-ventricular curve which marks a rising pressure just higher than the simultaneous pressure in the auricle or artery, may be taken to mark the closing of the cuspid valve or the opening of the semilunar valve, as the case may be. By a converse process, the moment of opening of the cuspid valve, or of closing of the semi-

<sup>1</sup> von Frey and Krehl: *op. cit.*, p. 61.



lunar, may also be ascertained. The practical difficulties in the way of applying this method to the ventricle and auricle are much greater than to the ventricle and artery. By another application of the principle just described, a "differential manometer" has been devised for the purpose of registering as a single curve the successive differences, from moment to moment, between the ventricular and auricular pressures, or the ventricular and arterial pressures (see Fig. 25). To this end, two elastic manometers are fastened immovably together, and their two elastic disks, instead of bearing upon separate levers, are made to bear upon a single one, which has its fulcrum between the disks, and is a lever not of the third order, but of the first, like a common balance.

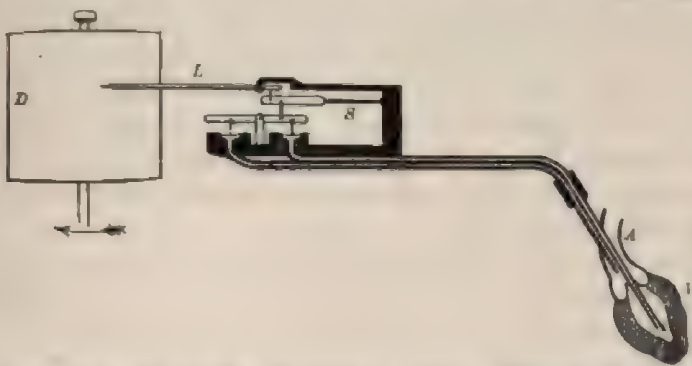


FIG. 25.—Diagram of the differential manometer: A, artery; V, ventricle; D, drum of kymograph, revolving in the direction of the arrow, and covered with smoked paper; L, recording lever in contact with the revolving drum; S, a spring by which the movement of the lever worked by the disks is transmitted to the recording lever. (The working details of the instrument are suppressed or altered for the sake of clearness.)

As the lever or beam of the balance turns from the horizontal as soon as the scales are pressed upon by unequal weights, so the lever of the differential manometer turns as soon as the disks are unequally affected by the pressures within the ventricle and the auricle, or the ventricle and the artery. As, however, the pressures upon the scales are from above, while those upon the disks are from below, the disk which tends to "kick the beam" is the one acted upon by the greater pressure, instead of by the less, as in the case of the scales. The manometric lever marks its oscillations as a curve upon the kymograph by the help of a second or "writing lever" connected with it. The persistence of exactly equal pressures, no matter what their absolute value, in the two manometers would cause a horizontal line to be drawn by the writing lever. This would serve as a base-line. The differential manometer is a valuable instrument, although it is evident that where such minute differences of space and time are recorded as a curve by such complicated mechanisms, the sources of error must be numerous and difficult to avoid.<sup>1</sup>

The methods which proceed by the measurement of differences of pressure may sometimes be controlled, or even replaced, by an easier method, as follows: If two manometers simultaneously record on the same kymograph the pressure-

<sup>1</sup> K. Hürthle: *Pflüger's Archiv für die gesammte Physiologie*, 1891, Bd. 49, S. 45.



curves of the ventricle and the auricle, or of the ventricle and the artery, any very sudden change of pressure, produced in auricle or artery at the opening or shutting of a cardiac valve, will produce a peak or angle in the curve of pressure of the auricle or artery. By the rules of the graphic method the point in the pressure-curve of the ventricle can easily be found which was written at the same instant with the peak or angle in the auricular or arterial curve. That point upon the ventricular curve, when marked, will indicate the instant of opening or shutting of the valve in question. In the pressure-curve obtained from the aorta close to the heart, there is a sudden angle which clearly marks the instant when the opening of the semilunar valve leads to the sudden rise of pressure which causes the up-stroke of the pulse (see Fig. 23). Again, the fluctuation of aortic pressure which we shall learn to know as the "dierotic wave" begins at a moment which many believe to follow closely upon the closure of the semilunar valve. That moment may be indicated by a notch in the aortic curve. So, too, the rise of pressure within the auricle produced by its systole may suddenly be succeeded by a fall, the beginning of which must mark the closure of the cuspid valve, which closure thus may correspond with the apex of the auricular curve.

In Figure 23, ordinate 1 indicates the closing, and ordinate 4 the opening, of the mitral valve. These two points were found by help of the differential manometer. Ordinate 2 indicates the opening, and ordinate 3 the closing, of the aortic valve. These two points were marked with the help of the curve of aortic pressure, also shown in Figure 23, each ordinate of which has the same number as the corresponding ordinate of the ventricular curve. In the arterial curve, 2 marks the beginning of the systolic rise, and 3 the beginning of the dierotic wave, which latter point is treated by the observer as closely corresponding to the closure of the aortic valve. In Figure 24 each ordinate has the same number, and, as regards the valve-play, the same significance, as in Figure 23. Ordinate 1 corresponds to the apex of a peak in the auricular curve (not here given) which represents the end of the auricular systole. Ordinate 2 corresponds to the beginning of the systolic ascent in the aortic curve (not here given). Ordinate 3 was found by comparing, by means of two elastic manometers, the simultaneous pressures in the ventricle and the aorta. Ordinate 4 corresponds, on the auricular pressure-curve, to a point which marks the beginning of a decline of pressure believed by the observer to succeed the opening of the cuspid valve. In both the figures given of the ventricular curve, and in such curves in general, the points which mark the valve-play occur as follows: The closure of the cuspid valve corresponds to a point, not far above the line of atmospheric pressure, where the moderate upward sweep of the ventricular curve takes on the steepness of the systolic ascent. The systole of the auricle is of little force, and the blood injected by it into the distensible ventricle raises the pressure there but little; that little, however, is more than the relaxing auricle presents, and the cuspid valve is closed. Somewhere on the steep systolic ascent occurs the point corresponding to the rise of the ven-

tricular above the arterial pressure, and therefore to the opening of the semilunar valve. But other forces beside the arterial pressure must be overcome by the contracting muscle; and the ventricular pressure mounts higher yet, and either stays high for a while, producing the plateau, or, in a peaked curve, at once descends. In either case, not long after the beginning of the sharp descent, the point occurs at which the ventricular pressure falls below the arterial, and the semilunar valve is closed. Beyond this point the curve continues steeply downward, but it is not till a point is reached not far above, or possibly even below, the atmospheric pressure that the pressure in the ventricle falls below that in the auricle, and the cuspid valve is opened.

**The Period of Reception, the Period of Ejection, and the Two Periods of Complete Closure of the Ventricle.**—During the whole of the period when the cuspid valve is open, the pressure is lower in the ventricle than in the artery; the arterial valve is shut; and blood is entering the ventricle. This may be called the “period of reception of blood.” During the greater part of the period when the cuspid valve is shut, the arterial valve is open; the pressure is higher in the ventricle than in the artery; and the ejection of blood from the former is taking place. This may be called the “period of ejection,” and lies in Figures 23 and 24 between the ordinates 2 and 3. The careful work which has enabled us to mark the valve-play upon the ventricular curve has demonstrated the interesting fact that there occur two brief periods during each of which both valves are shut, and the ventricle is a closed cavity. Of these two periods, one immediately precedes the period of ejection, and the other immediately follows it. The first lies, in Figures 23 and 24, between the ordinates 1 and 2; the second, between 3 and 4. The explanation of these two periods is simple. It takes a brief but measurable time for the cardiac muscle, forcibly contracting upon the imprisoned liquid contents of the closed ventricle, to raise the pressure to the high point required to overcome the opposing pressure within the artery and to open the semilunar valve. Again, it takes a measurable time, probably seldom quite so brief as the period just discussed, for the cardiac muscle to relax sufficiently to permit the pressure in the closed ventricle to fall to the low point required for the opening of the cuspid valve. The ventricular cycle, thus studied, falls into four periods: the first is a brief period of complete closure with swiftly rising pressure; the second is the period of ejection, relatively long, and but little variable; the third is a period of complete closure, with swiftly falling pressure; the fourth is the period when the pressure is low and blood is entering the ventricle. This last period is very variable in length, but at the average pulse-rate it is the longest period of all.

**Phenomena of the Period of Reception of Blood.**—We have already followed the course of the pressure within the ventricle from the moment of opening of the auriculo-ventricular valve to that of its closing (p. 128). During this time the ventricle is receiving its charge of blood, the flaccidity of the wall rendering expansion easy and keeping the pressure low. The blood which enters first has been accumulating in the auricle since the closing of the



cuspid valve, and now, upon the opening of this, it both flows and is to some slight degree drawn into the ventricle. This blood is followed by that which, during the remainder of the "repose of the whole heart," moves through the veins and the auricle into the ventricle under the influence of the arterial recoil and the other forces which cause the venous flow (p. 93); and the charge of the ventricle is completed by the blood which is injected at the auricular systole.

**The Negative Pressure within the Ventricles.**—That the heart, in its diastole, draws something from without into itself is a very ancient belief, and this mode of its working played a great part in the doctrines of Galen and of the Middle Ages. In 1543, Vesalius, who, on anatomical grounds, questioned some of Galen's views as to the cardiac physiology, fully accepted this one.<sup>1</sup> On the other hand, in 1628, Harvey rejected it. "It is manifest," he says, "that the blood enters the ventricles not by any attraction or dilatation of the heart, but by being thrown into them by the pulses of the auricles."<sup>2</sup> In this particular, modern research in some degree confirms the opinion of the ancients, while denying to suction within the ventricles any such great effect as was once believed in. As a rule, the cuspid valve is not opened till the pressure in the ventricle has fallen to a point not far from the pressure of the atmosphere; it may be even below it. In any case the ventricular pressure usually becomes negative very soon after the opening of the cuspid valve. This negative pressure is of variable extent and continues for a variable time. It is always small as compared with the positive pressure of the systole. Under some circumstances negative pressure may be absent, but it is so very commonly present as certainly to be a normal phenomenon (see Figs. 22, 23, and 24). This negative pressure is revealed by the elastic as well as by the minimum mercurial manometer; it is present in both ventricles; and it is present, to a less degree, even after the chest has been opened, and its aspiration destroyed. It is in virtue of the forces which produce the negative pressure in the manometer that blood is drawn into the heart.

Passing by disproven or improbable theories as to the causes of this suction, we shall find the following statements justified: As the heart lies between the lungs and the chest-wall (including in this term the diaphragm), it is subject, like the chest-wall and the great vessels, to the continuous aspiration produced by the stretched fibres of the elastic lungs. At every inspiration this aspiration is increased by the contraction of the inspiratory muscles. We see, therefore, that the ventricle must overcome this aspiration as part of the resistance to its contraction; and that, as soon as that contraction has ceased, the walls of the ventricle must tend to be drawn asunder by those same forces of elastic recoil in the pulmonary fibres, and of contraction of the muscles of inspiration, which we have seen (p. 95) to produce a slight suction within the great veins in and

<sup>1</sup> *Andree Vesalii Bruzellensis, Scholæ medicorum Patavinæ professoris, de Humani corporis fabrica Libri septem.* Basileæ, ex officina Ioannis Oporini, Anno Salutis reparate MDXLIII. Page 587.

<sup>2</sup> *Op. cit.*, 1628, p. 26: Willis's translation, Bowie's edition, 1889, p. 28.



very near the chest. These same forces produce a slight suction within the ventricles, relaxed in their diastole. But a very slight suction occurs at each ventricular diastole even after the chest has been opened. The causes of this are still obscure; but it is to be borne in mind that the relaxing wall of the ventricle, flabby as it is, possesses some little elasticity, especially at the auriculo-ventricular ring, and therefore may tend to resume a somewhat different form from that due to its contraction. As the result of this slight elastic recoil, a feeble suction may occur.

#### N. THE FUNCTIONS OF THE AURICLES.

**Connections of the Auricle.**—Into the right and left auricles open the systemic and pulmonary veins respectively, and each auricle may justly be regarded as the enlarged termination of that venous system with which it is connected. Until modern times the terms of anatomy reflected this view, and from the ancient Greeks to a time later than Harvey, the word "heart" commonly meant the ventricles only, as it still does in the language of the slaughter-house. This termination of the venous system, the auricle, communicates directly with the ventricle, at the auriculo-ventricular ring, by an aperture so wide that, when the cuspid valve is freely open, auricle and ventricle together seem to form but a single chamber.

**The Auricle a Feeble Force-pump; the Pressure of its Systole.**—The wall of the auricle is thin and distensible; it is also muscular and contractile. But the slightest inspection of the dead heart shows how little force can be exerted by the contraction of so thin a sheet of muscle. In the wall of the appendix, however, the muscular structure is more vigorously developed than over the rest of the auricle. The auricle, then, should be a very feeble force-pump; and such in fact, it is; for the highest pressure scarcely rises above 20 millimeters of mercury in the right auricle of the dog,<sup>1</sup> and an auricular systole often produces a pressure of only 5 or 10 millimeters.<sup>2</sup> This would be but a small fraction of the maximum ventricular pressure of the same heart. The auricle, however, is equal to its work of completing the filling of the ventricle; and the feebleness of the auricle will not surprise us when we consider that, at the beginning of its systole, the pressure exerted by the contents of the relaxed ventricle is but little above that of the atmosphere, and offers small resistance to the injection of an additional quantity of blood.

The systole of the auricles is so conspicuous a part of the cardiac cycle when the beating heart is looked at, that its necessity is easily overrated. Even Harvey, in attacking the errors of his day, was led by imperfect methods to estimate too highly the work of the auricular systole (see p. 134). The error, although a gross one, is not rare, of considering the systole of the auricles to be as important for the charging of the ventricles as the systole of the ventricles is for the charging of the arteries. On page 98 the proof has already been given

<sup>1</sup> Goltz and Gaule: *op. cit.*, p. 106.

<sup>2</sup> W. T. Porter: *op. cit.*, p. 533. S. de Jager: *op. cit.*, p. 506.

that the work of the heart may entirely suffice to maintain the circulation without aid from any subsidiary source of energy. It must now be added that the ventricles can, for a time, maintain the circulation without the aid of the auricular systole—a clear proof that this systole is not a *sine qua non* for the working of the cardiac pump.

If in an animal, not only anesthetized but so drugged that all its skeletal muscles are paralyzed, artificial respiration be established and the chest be opened, the circulation continues. If the artificial respiration be suspended for a time, the lungs collapse, asphyxia begins, and the blood accumulates conspicuously in the veins and in the heart. Presently the muscular walls of the auricles may become paralyzed by overdistention, and their systoles may cease, while the ventricles continue at work and may maintain a circulation, although of course an abnormal one. After the renewal of artificial respiration, it may not be till several beats of the ventricles have succeeded, without help from the auricles, in unloading the latter and the veins, that the auricles recommence their beats.<sup>1</sup>

On the other hand, it is clear that the auricle is not without importance as a force-pump for completing the filling of the ventricle, even if it can be dispensed with for a time. In curves of the blood-pressure during asphyxia taken simultaneously from the auricle and the ventricle, there may be noted the influence exerted upon the ventricular curve by ineffectiveness of the auricular systole. It is found that, in this case, that slight but accelerated rise of pressure may fail which normally just precedes, and merges itself in, the large swift rise of the ventricular systole. It is found, too, that, under these circumstances, the total height of this systolic rise may be diminished.<sup>2</sup> We shall see presently how, when the pulse becomes very frequent, the importance of the auricular systole may be increased. We have seen already (p. 132) that normally it may probably effect the closure of the cuspid valves.

**Time-relations of the Auricular Systole and Diastole.**—The auricular systole is not only weak, but brief, being commonly reckoned at about 0.1 of a second (see p. 124). If this be correct for man, at the average pulse-rate of 72 the auricular systole would comprise only about one-eighth of the cycle; would be only one-seventh as long as the auricular diastole; and only about one-third as long as the ventricular systole which immediately follows that of the auricle.

**The Auricle a Mechanism for Facilitating the Venous Flow and for the "Quick-charging" of the Ventricle.**—Further points in regard to the systole of the auricles can best be treated of incidentally to the general question, What is the principal use of this portion of the heart? The answer is not so obvious as in the case of the ventricles. It may, however, be stated as follows: The auricle is a reservoir, lying at the very door of the ventricle. That door, the cuspid valve, remains shut during the relatively long and unvarying period of the ventricular systole and the brief succeeding period of fall-

<sup>1</sup> von Frey und Krehl: *op. cit.*, pp. 49, 59. G. Colin: *Traité de physiologie comparée des animaux*, Paris, 1888, vol. ii. p. 424.

<sup>2</sup> von Frey und Krehl: *op. cit.*, p. 59.



ing pressure within the ventricle. These periods coincide with the earlier part of the auricular diastole. During all this time the forces which cause the venous flow are delivering blood into the flaccid and distensible reservoir of the auricle, and can thus maintain a continuous flow. But the blood of which the veins are thus relieved during the period of closure of the cuspid valve, accumulates just above that valve to await its opening. When it is opened by the superior auricular pressure, the stored-up blood both flows and is drawn into the ventricle promptly from the adjoining reservoir. From this time on, auricle and ventricle together are converted into a common storehouse for the returning blood during the remainder of the repose of the whole heart, which coincides with the later portion of the long auricular diastole. The next auricular systole completes the charging of the ventricle; and a second use of this systole now becomes apparent, for the sudden transfer by it of blood from auricle to ventricle not only completes the filling of the latter, but lessens the contents of the auricle, and so prepares it to act as a storehouse during the coming systole of the ventricle. The auricle, then, is an apparatus for the maintenance of as even a flow as possible in the veins and for the rapid and thorough charging of the ventricle. It is clear that, for both uses, the auricle's function as a reservoir is certainly no less important than its function as a force-pump.

The value of a mechanism for the rapid filling of the ventricle increases with the pulse-rate, and with a very frequent pulse must be of great importance, because now time must be saved at the expense of the pause, with its quiet flow of blood through the auricle into the ventricle; and the auricular systole must follow more promptly than before upon the opening of the cuspid valve. If the pulse double in frequency, each cardiac cycle must be completed in one-half the former time; but we have seen that the ventricle requires for its systole a time which cannot be shortened with the cycle to the same degree as can its diastole. Of heightened value now to the ventricle will be the adjoining reservoir, which is filling while the cuspid valve remains closed, and from which, as soon as that valve is opened, the necessary supply not only flows, but is sucked and pumped into the ventricle, for, when increased demands are made upon the heart, the usefulness of an increased frequency of beat disappears if the volume transferred at each beat from veins to arteries diminish in the same proportion as the frequency increases. No increase of the capillary stream can then follow the more frequent strokes of the pump.<sup>1</sup>

**Negative Pressure within the Auricle; its Probable Usefulness.**—The course of the pressure-curve of the auricle, as shown by the elastic manometer, is too complex and variable, and its details are too much disputed, for it to be given here. But certain facts regarding the auricular pressure are of much interest in connection with the use of the auricle which has just been discussed. Once, and perhaps oftener, in each cycle, the pressure in the auricle may become negative, perhaps to the degree of from  $-2$  to  $-10$  millimeters of mercury even in the open chest,<sup>2</sup> and of course becomes still more so when

<sup>1</sup> von Frey und Krehl: *op. cit.*, p. 61.

<sup>2</sup> de Jager: *op. cit.*, p. 507. W. T. Porter: *op. cit.*, p. 533.



the latter is intact, sinking in this case to perhaps —11.2 millimeters.<sup>1</sup> What is striking in connection with the "quick-charging" of the ventricle is that the greatest and longest negative pressure in the auricle coincides, as we should expect, with the earlier part of its diastole, and therefore with the systole of the ventricle, when the auricle is cut off from it by the shut valve.<sup>2</sup> By this suction within the auricle the flow from the veins into it probably is heightened, and the store of blood increased which accumulates in the reservoir to await the opening of the valve. The quick-charging mechanism itself is quickly charged. Nor should it be forgotten that the work of the ventricle contributes in some degree to this suction within the auricle. The heart is air-tight in the chest, which is a more or less rigid case. At each ventricular systole the heart pumps some blood out of this case, and shrinks as it does so, thus tending to produce a vacuum; in other words, to increase the amount of negative pressure within the chest, and thus help to expand the swelling auricles. Therefore for the suction which helps to charge the auricles during the systole of the ventricles, that systole itself is partly responsible.<sup>3</sup>

**Is the Auricle Emptied by its Systole?**—Authorities differ still as to the extent to which the auricle is emptied by its systole; some holding the scarcely probable view that, during this time, its contents are all, or nearly all, transferred to the ventricle;<sup>4</sup> and others taking the widely different view that the auricle actually continues to receive blood during its systole, which latter simply increases the discharge into the ventricle. According to this latter opinion the flow from the great veins into the auricle is absolutely unbroken.<sup>5</sup> All are agreed, however, that the auricular appendix is the most completely emptied portion of the chamber.

**Are the Venous Openings into the Auricle closed during its Systole? If not, does Blood then regurgitate, or enter?**—As to these questions differences of opinion are possible, because at the openings of the veins into the auricle no valves exist which are effective in the adult, except at the mouth of the coronary sinus. It is therefore a question, what happens at the mouths of the veins during the auricular systole. These mouths are surrounded by rings composed of the muscular fibres of the auricular wall; and for some distance from the heart the walls of some of the great veins are rich in circular fibres of muscle. We have seen already (p. 115) that a rhythmic contraction of the venæ cavæ and pulmonary veins occurs just before the systole of the auricles and must accelerate the flow into the latter. Their swiftly following systole is known to begin at the mouths of the great veins and from these to spread over the rest of each auricle. It is evident at once that the circular fibres must

<sup>1</sup> Goltz und Gaule: *op. cit.*, p. 109.

<sup>2</sup> von Frey und Krehl: *op. cit.*, p. 53; W. T. Porter: *op. cit.*, p. 523.

<sup>3</sup> A. Mosso: *Die Diagnostik des Pulses*, etc. Zweiter Theil: Ueber den negativen Puls, S. 42.

<sup>4</sup> M. Foster: *A Text-book of Physiology*, New York, 1896, p. 182.

<sup>5</sup> Skoda: "Ueber die Function der Vorkammern des Herzens," *Sitzungsberichte der mathem.-naturw. Classe der kais. Akademie der Wissenschaften in Wien*, 1852, Bd. ix. S. 788. L. Hermann: *Lehrbuch der Physiologie*, 1900, S. 66.

either narrow or obliterate, like sphincters, the mouths of the veins at the outset of the systole, and that these fibres thus take the place of valves. If the closure be complete, all the blood ejected by the systole must enter the ventricle, and a momentary standstill of blood and rise of pressure in the veins just without the auricle must accompany its brief systole. A recent observer believes the flow into the auricle to be interrupted even more than once during its cycle.<sup>1</sup> If the venous openings be not closed but only narrowed during the systole of the auricles, the transfer of all or most of the ejected blood to the ventricle must depend upon the pressure being lower therein than at the venous openings. A slight regurgitation into the veins would, like the complete closing of their mouths, cause a momentary checking of their blood-flow just without the auricle, and a slight rise of pressure. Such a checking of the flow has in some cases been observed and ascribed to regurgitation.<sup>2</sup> A systolic narrowing without closure of the venous mouths would leave room also for the view already given, that so far is regurgitation from taking place, that even during the systole of the auricles blood enters them incessantly, and the venous flow is never checked. In this case the systole of the auricle would still empty it partially into the ventricle, owing to the lowness of the pressure there.

The time has not arrived for a decision as to all these questions, which are surrounded by practical difficulties; but fortunately they do not throw doubt upon the functions of the auricle as a reservoir and pump which may be swiftly filled, and may swiftly complete the filling of the ventricle which it adjoins.

#### O. THE ARTERIAL PULSE.

**Nature and Importance.**—The expression "arterial pulse" is restricted commonly to those incessant fluctuations of the arterial pressure which correspond with the incessant beatings of the ventricles of the heart. These rhythmic fluctuations of the arterial pressure have been explained already (p. 92) to depend upon the rhythmic intermittent injections of blood from the ventricles; upon the resistance to these injections produced by the friction within the blood-vessels; and upon the elasticity of the arterial walls. It has also been explained that the interaction of these three factors is such that the blood, in traversing the capillaries, comes to exert a continuous pressure, free from rhythmic fluctuations; in other words, that the pulse undergoes extinction at the confines of the arterial system. It is at once apparent that the pulse may be affected by an abnormal change, either in the heart's beat, in the elasticity of the arteries, or in the peripheral resistance, or by a combination of such changes; and that, therefore, the characters of the pulse possess an importance in medical diagnosis which justifies a brief further discussion of them.

**A pulsating artery not only expands, but is lengthened.** The sudden

<sup>1</sup> W. T. Porter: *op. cit.*, p. 534.

<sup>2</sup> François-Franck: "Variations de la vitesse du sang dans les veines sous l'influence de la systole de l'oreillette droite," *Archives de physiologie normale et pathologique*, 1890, p. 347.



increase in the contents of an artery which causes the pulse therein, is accommodated not merely by the increase of calibre which produces the "up-stroke" of the arterial wall against the finger, but also by an increase in the length of the elastic vessel. If the artery be sinuous in its course, this increase in length suddenly exaggerates the curves of the vessel, and thus produces a slight wriggling movement. This is sometimes very clearly visible in the temporal arteries of emaciated persons. On the other hand, the increase in the calibre of the artery is relatively so slight that it is invisible at the profile even of a large artery, dissected clean for a short distance for the purpose of tying it. Such a vessel appears pulseless to the eye, although its pulse is easily felt by the finger, which slightly flattens the artery and thus gains a larger surface of contact.

**Transmission of the Pulse.**—If an observer feel his own pulse, placing the finger of one hand upon the common carotid artery, and that of the other upon the dorsal artery of the foot at the instep, he will perceive that the pulse corresponding to a given heart-beat occurs later in the foot than in the neck. This phenomenon is readily comprehended by considering that room for the "pulse-volume" injected by the heart is made in the root of the arterial system both by local expansion and by a more rapid displacement of blood into the next arterial segment. This next segment, in turn, accommodates its increased charge by local expansion and by a more rapid displacement; and this same process involves segment after segment in succession, onward toward the capillaries. The expansion of the arterial system, then, is a progressive one, and, as the phrase is, spreads as a wave from the aorta onward to the arterioles. The rate of transmission of the "pulse-wave" from a point near the heart to one remote from it, may be calculated. This is done by comparing the time which elapses between the occurrence of the up-stroke of the pulse in the nearer and in the farther artery with the distance along the arterial system which separates the two points of observation. In one case, for example, that of an adult, the absolute amount of the postponement of the pulse—that is, the time required for the transmission of the pulse-wave from the heart itself to the *arteria dorsalis pedis*, was 0.193 second.<sup>1</sup> The time of transmission of the pulse-wave from the heart to the *dorsalis pedis* is often longer than in this case, amounting to 0.2 second or a little more. If we reckon the duration of the ventricular systole at about 0.3 second, it is evident that the fact of the postponement of the pulse in the arteries distant from the heart does not invalidate the general statement that the arterial pulse is synchronous with the systole of the ventricles.

The general estimates of the rate, as opposed to the absolute time, of transmission of the pulse-wave vary, in different cases, from more than 3 meters to more than 9 meters per second. \*As the blood in the arteries does not pass onward at a swifter rate than about 0.5 meter per second, it is clear that the wave of expansion moves along the artery many times faster than the blood does; and that to confound the travelling of the wave with the travelling of

<sup>1</sup> J. N. Czermak: *Gesammelte Schriften*, 1879, Bd. i. Abth. 2, S. 711.



the blood would be a very serious error, easily avoided by bearing in mind the causes of the pulse-wave as already given.

**Investigation by the Finger.**—The feeling of the pulse has been a valuable and constantly used means of diagnosis since ancient times. Indeed, the ancient medicine attached to it more importance than does the practice of to-day. But it is still advisable to warn the beginner that he may not look to the pulse for "pathognomonic" information; that is to say, he may not expect to diagnose a disease solely by touching an artery of the patient under examination. The pulse is most commonly felt in the radial artery, which is convenient, superficial, and well supported against an examining finger by the underlying bone. Many other arteries, however, may be utilized.

**Frequency and Regularity.**—The most conspicuous qualities of the pulse are frequency and regularity. Usually these can be appreciated not merely by a physician but by any intelligent person. The physiological variations in the frequency of the heart's beats have been referred to already (p. 121). In an intermittent pulse the rhythm is usually regular, but, at longer or shorter intervals, the ventricle omits a systole, and therefore, the pulse omits an up-stroke. Either intermittence or irregularity of the cardiac beats may be caused by transient disorder as well as by serious disease.

**Tension.**—When unusual force is required in order to extinguish the pulse by compressing the artery against the bone, the arterial wall, and hence the pulse, is said to possess high tension, or the pulse is called incompressible, or hard. Conversely, the pulse is said to be of low tension, compressible, or soft, when its obliteration is unusually easy. A very hard pulse is sometimes called "wiry;" a very soft one, "gaseous." High tension, hardness, incompressibility, obviously are directly indicative of a high blood-pressure in the artery; and the converse qualities of a low pressure. It follows from what has gone before that the causes of changes in the arterial pressure, and hence in the tension, may be found in changes either in the heart's action, or in the peripheral resistance, or, as is very common, in both. An instrument called a sphygmomanometer<sup>1</sup> or sphygmometer is sometimes applied to the skin over the artery, in order to obtain a better measurement of its hardness or softness, and hence of the blood-pressure within it, than the finger can make. Such instruments are not free from sources of error.

**Size.**—When the artery is unusually increased in calibre at each up-stroke of the pulse, the pulse is said to be large. When, at the up-stroke, the calibre changes but little, the pulse is said to be small. A very large pulse is sometimes called "bounding;" a very small one, "thready." Largeness of the pulse must be distinguished carefully from largeness of the artery. The former phrase means that the fluctuating part of the arterial pressure is large in proportion to the mean pressure. But if the mean pressure be great while the fluctuating part of the pressure is relatively small, the artery, even at the end of the down-stroke, will be of large calibre, while the pulse will be small.

<sup>1</sup> From *σφυγμός*, pulse.

It has been seen that the increased charge of blood which an artery receives at the ventricular systole is accommodated partly by increased displacement of blood toward the capillaries, and partly by that increase in the capacity of the artery which is accompanied by the up-stroke of the pulse. The less the contents of the artery the less is the arterial pressure, the less the tension of the wall, and the more yielding is that wall. The more yielding the wall, the more of the increased charge of blood does the artery accommodate by an increase of capacity and the less by an increase of displacement. Therefore, a large pulse often accompanies a low mean pressure in the arteries, and hence may appear as a symptom after large losses of blood. In former days, when bloodletting was practised as a remedial measure, imperfect knowledge of the mechanics of the circulation sometimes caused life to be endangered; for a "throbbing" pulse in a patient who had been bled already was liable to be taken as an "indication" for the letting of more blood. If this were done, an effect was combated by repeating its cause.<sup>1</sup>

**Celerity of Stroke.**—When each up-stroke of the pulse appears to be slowly accomplished, requiring a relatively long interval of time, the pulse is called slow, or long. When each up-stroke appears to be quickly accomplished, requiring a relatively short time, the pulse is called quick or short. These contrasted qualities are among the most obscure of those which the skilled touch is called upon to appreciate.

**The Pulse-trace.**—The rise and fall of a pulsating human artery, if near enough to the skin, may be made to raise and lower the recording lever of a somewhat complicated instrument called a sphygmograph.<sup>2</sup> Of this instrument a number of varieties are in use. If the fine point of the lever be kept in contact with a piece of smoked paper which is in uniform motion, a "pulse-trace" or "pulse-curve" is inscribed, which shows successive fluctuations, larger and smaller, which tend to be rhythmically repeated, and which depend upon the movements of the arterial wall produced by the fluctuations of blood-pressure. In an animal, a manometer may be connected with the interior of an artery, and thus the fluctuations of the blood-pressure may be observed more directly. It has been explained (p. 90) that the mercurial manometer is of no value for the study of the finer characters of the pulse, owing to the inertia of the mercury. On the other hand, the best forms of elastic manometer give pulse-traces which are more reliable than those of the sphygmograph. This is because the sphygmographic trace is subject to unavoidable errors dependent upon the physical qualities of the skin and other parts which intervene between the instrument and the cavity of the artery. Nevertheless, the sphygmographic pulse-trace, or "sphygmogram," is the only pulse-trace which can be obtained from the human subject; and, when obtained from an animal, it has so much in common with the trace recorded by the elastic manometer, that the sphygmograph has been much used for the study of the human pulse, in health and disease, both by physiologists and by

<sup>1</sup> Cf. Lodi Hall. *Researches principally relative to the Morbid and Curative Effects of Loss of Blood*. London, 1856.

<sup>2</sup> From σφυγμός, pulse, and γραφειν, to record.



medical practitioners. As a means of diagnosis, however, the sphygmogram still leaves much to be desired. The same instrument, applied in immediate succession to different arteries of the same person, gives, as might be expected, pulse-traces of somewhat different forms. The same artery of the same person yields to the same instrument at different times different forms of trace, depending upon different physiological states of the circulation. But the same artery yields traces of different form to sphygmographs of different varieties applied to it in immediate succession; and even moderate changes in adjustment cause differences in the form of the successive traces which the same instrument obtains from the same artery. It is no wonder, therefore, that great care must be exercised in comparing sphygmographic observations, and in drawing general conclusions from the information which they impart.

**The Details of the Sphygmogram.**—Figure 26 is a fair example of the sphygmograms commonly obtained from the healthy human radial pulse. When this trace was taken, the subject's heart was beating from 58 to 60 times



FIG. 26.—Sphygmogram from a normal human radial pulse beating from 58 to 60 times a minute. To be read from left to right (Burdon-Sanderson).

a minute. The trace records the effects upon the lever of five successive complete pulsations of the artery, which all agree in the general character of their details, while differing in minor respects. By the tracing of each pulsation the up-stroke is shown to be sudden, brief, and steady, while the down-stroke is gradual, protracted, and oscillating. The commencing recoil of the arterial wall succeeds its expansion with some suddenness. In many sphygmograms this is exaggerated by the inertia of the instrument. As shown by the trace represented in the figure, and by most such traces, the recoil soon changes from rapid to gradual, and, in the trace, its protracted line becomes wavy, indicating that the slow diminution of calibre varies its rate, or even is interrupted by one or more slight expansions, before it reaches its lowest, and is succeeded by the up-stroke of the next pulsation. In each of the five successive pulsations the traces of which are shown in Figure 26, the line which represents the more gradual portion of the down-stroke of the pulse is made up of three waves, of which the first is the shortest, the last the longest and lowest, and the middle one intermediate in length, but by far the highest. This middle wave is, in fact, the only one of the three to produce which an actual rise of pressure occurs; in each of the other two, no rise, but only a diminished rate of decline, is exhibited. The changes of pressure which produce the first and third of the waves just spoken of, in the pulse-trace under consideration, are very obscure in their origin, and are inconstant in their occurrence, sometimes being more numerous than in the trace shown in Fig. 26, and sometimes failing altogether to appear.

**The Dicrotic Wave.**—The oscillation of pressure, however, which pro-



duces the middle wave of each of the pulsations of Figure 26, is so constant in its occurrence that it is undoubtedly a normal and important phenomenon, although, in different sphygmograms, the height, and position in the trace, of the wave inscribed by this oscillation may vary. Occasionally this oscillation is morbidly exaggerated, so that it may be not only recorded by the sphygmograph, but even felt by the finger, as a second usually smaller up-stroke of the pulse. In such a case the artery is felt to beat twice at each single beat of the ventricle, and is said, technically, to show a "dicrotic"<sup>1</sup> pulse. Where a dicrotic pulse can be detected by the finger, it is apt to accompany a markedly low mean tension of the arterial wall. The dicrotic pulse was known, and named, long before the sphygmograph revealed the fact that the pulse is always dicrotic, although to a degree normally too slight for the finger to appreciate. The sphygmographic wave which records the slight "dicrotism" of the normal pulse is called the "dicrotic wave." Where dicrotism can be felt by the finger, the sphygmogram naturally exhibits a very conspicuous dicrotic-wave.

The origin of the dicrotic oscillation has been much discussed, and is not yet thoroughly settled, important as a complete settlement of it would be to the true interpretation and clinical usefulness of the sphygmogram. It is believed by some that this fluctuation of pressure is produced at the smaller arterial branches, as a reflection of the main pulse-wave, and that the dicrotic wave, thus reflected, travels toward the heart, and, naturally, reaches a given artery after the main wave of the pulse has passed over it, travelling in the opposite direction. The weight of probability, however, is in favor of the view that the dicrotic wave essentially depends upon a slight rise of the arterial pressure, or slackening of its decline, due to the closing of the semi-lunar valve; and that, therefore, this wave follows the main wave of arterial expansion outward from the heart, instead of being reflected inward from the periphery. If the dicrotic wave be caused solely by reflection from the periphery, it ought, in a sphygmogram from a peripheral artery, to begin at a point nearer to the highest point of each pulsation than in the case of an artery near the heart, in which latter vessel, naturally, a reflected wave would undergo postponement. On the other hand, if the dicrotic wave be transmitted toward the periphery, and caused solely by the closure of the aortic valve, it ought, in a sphygmogram from a peripheral artery, to occupy very nearly the same relative position as in a sphygmogram taken from an artery near the heart. But a wave running toward the periphery may be modified by a reflected wave in the same vessel, and a reflected wave may undergo a second reflection at the closed aortic valve, or even elsewhere, and thus give rise to an oscillation which will be transmitted toward the periphery. These statements show with what technical difficulties the subject is beset, whether the sphygmograph be employed, or, in the case of animals, the elastic manometer, the traces recorded by which also exhibit the dicrotic wave. As

<sup>1</sup> From *δίκροτος*, double-beating.

already stated, however, the probabilities are in favor of the valvular origin of the dicrotic wave.

If it be true that the closure of the aortic valve causes the dicrotic wave, the instant marked by the commencement of this wave, in the manometric trace inscribed by the pressure within the first part of the arch of the aorta itself, practically marks the instant of closure of the aortic valve. We have seen (p. 130) that this doctrine has been made use of in the elucidation of the curve of the pressure within the ventricle.

**The Diagnostic Limitations of the Sphygmogram.**—The feeling of the pulse, imperfect as is the most skilled touch, cannot be replaced by the use of the sphygmograph. The presence, between the cavity of the artery and the surface of the body, of a quantity of tissue the amount and elasticity of which differ in different people, and even differ over neighboring points of the same artery, renders it impossible so to adjust the spring of the sphygmograph as to be able to obtain a reliable base-line corresponding to the abscissa, or line of atmospheric pressure, in the case of the manometric curve of blood-pressure. The effects produced by slight differences in the placing of the instrument tend to the same result. By the absence of such a base-line the sphygmographic curve is shorn of quantitative value as a curve of blood-pressure, and cannot give information as to whether, in clinical language, the pulse be hard or soft, large or small. Nor can a long or short pulse be identified from the appearance of the sphygmogram.<sup>1</sup> The pulse-trace still requires much elucidation; but when further study shall have rendered clearer the true extent, the normal variations, and the causes of the complex and incessant oscillations of the walls of the arteries, it may well be believed that both physiology and practical medicine will have gained an important insight into the laws of the circulation of the blood.

#### P. THE MOVEMENT OF THE LYMPH.

**The Lymphatic System.**—The lymph is contained within the so-called lymphatic system, the nature of which may be summarized as follows:

The lymph appears first in innumerable minute irregular gaps in the tissues, which gaps communicate in various ways with one another, and with minute lymphatic vessels, which latter, when traced onward from their beginnings, presently assume a structure comparable to that of narrow veins with very delicate walls and extremely numerous valves. These valves open away from the gaps of the tissues, as the valves of the veins open away from the capillaries. The lymphatic vessels unite to form somewhat larger ones, each of which, however, is of small calibre as compared with a vein of medium size, until at length the entire system of vessels ends, by numerous openings, in two main trunks of very unequal importance, the thoracic duct and the right lymphatic duct. The latter is exceedingly short, and receives the terminations of the lymphatics of a very limited portion of the body; the terminations of all the rest, including the lymphatics of the alimentary canal, are

<sup>1</sup> M. von Frey: *Die Untersuchung des Pulses*, 1892, S. 35.



received by the thoracic duct, which runs the whole length of the chest. Both of the main ducts have walls which, relatively, are very thin; and, like the smaller lymphatics, the ducts are abundantly provided with valves so disposed as to prevent any regurgitation of lymph from either duct into its branches. Each duct terminates on one side of the root of the neck, where, in man, the cavity of the duct joins by an open mouth the confluence of the internal jugular and subclavian veins where they form the innominate vein. At the opening of each duct into the vein a valve exists, which permits the free entrance of lymph into the vein, but forbids the entrance of blood into the duct.

It is a peculiarity of the lymphatic system that some of its vessels end and begin by open mouths in the so-called serous cavities of the body—those vast irregular interstices between organs the membranous walls of which interstices are known as the peritoneum, the pleuræ, and the like. For present purposes, therefore, these serous cavities may be regarded as vast local expansions of portions of the lymph-path. Another peculiarity of the lymphatic system depends upon the presence of the lymphatic glands or ganglia, which also are intercalated here and there between the mouths of lymphatic vessels which enter and leave them. The nature and importance of these bodies have been referred to in dealing with the origin of the leucocytes and the nature of the lymph (p. 47). For the present purposes the ganglia are of interest in this, that the lymph which traverses their texture meets, in so doing, with much resistance from friction. Physiologically, therefore, the lymph-path as a whole, extending from the tissue-gaps to the veins at the root of the neck, both differs from, and in some respects resembles, the blood-path from the capillaries to the same point.

The origin of the lymph has been discussed already (p. 71), and has been found to be partly from the blood in the capillaries, and partly from the tissues, to say nothing of the products directly absorbed from the alimentary canal during digestion. The quantity of material which leaves the lymph-path and enters the blood during twenty-four hours is undoubtedly large, amounting, in the dog, to about sixty cubic centimeters for each kilogram of body-weight. The movement of the lymph is, therefore, of physiological importance; and the causes of this movement must now be considered.

**Differences of Pressure.**—It is a striking fact that in man and the other mammals there exist no “lymph-hearts” for the maintenance of the lymphatic flow. The fundamental causes of the movement of the lymph are that at the beginning of its path in the gaps of the tissues it is under considerable pressure; that at the end of its path at the veins of the neck it is under very low pressure, which often, if not usually, is negative; and that throughout the lymph-path the valves are so numerous as to work effectively against regurgitation. The pressure of the lymph in the gaps of the tissues has been estimated at one half, or more, of the capillary blood-pressure,<sup>1</sup> which latter has been stated (p. 84) to be from 24 to 54 millimeters

<sup>1</sup> A. Landerer: *Die Gewebsspannung in ihrem Einfluss auf die örtliche Blut- und Lymphbewegung*, Leipzig, 1884, S. 103.



of mercury. The difference between one half of either of these pressures and the pressure in the veins of the neck, which pressure is not far from zero, is quite enough to produce a flow from the one point to the other. To this flow a resistance is caused by the friction along the lymph-path, which resistance causes the lymph to accumulate in the gaps of the tissues, and the pressure there to rise, until the tension of the tissues resists further accumulation more forcibly than friction resists the onward movement of the lymph. The little-known forces which continually produce fresh lymph, and pour it into the tissue-gaps against resistance, cannot be discussed here further than has been done in treating of the origin of the lymph (p. 71).

**Thoracic Aspiration.**—The causes have already been stated fully of that low, perhaps negative, pressure in the veins at the root of the neck which renders possible the continuous discharge of the lymph into the blood (p. 95). It need only be noted here that when inspiration rhythmically produces, or heightens, the suction of blood into the chest, it must also produce, or heighten, the suction of lymph out of the mouths of the thoracic and right lymphatic ducts. Moreover, as the thoracic duct lies with most of its length within the chest, each expansion of the chest must tend to expand the main part of the duct, and thus to suck into it lymph from the numerous lymphatics which join the duct from without the chest; while the numerous valves in the duct must promptly check any tendency to regurgitation from the neck.

**The Bodily Movements and the Valves.**—Like the flow of the blood in the veins, the flow of the lymph in its vessels is powerfully assisted by the pressure exerted upon the thin-walled lymphatics by the contractions of the skeletal muscles; for the very numerous valves of the lymphatics render it impossible for the lymph to be pressed along them by this means in any other than the physiological direction toward the venous system. Experiment shows that even passive bending and straightening of a limb in which the muscles remain relaxed, increases to a very great extent the discharge of lymph from a divided lymphatic vessel of that limb. It is probable, therefore, that movement in any external or internal part of the body, however produced, tends to relieve the tension in the tissues by pressing the lymph along its path.

**Conclusion.**—The movement of the lymph produced in these various ways is doubtless irregular; but a substance in solution, injected into the blood, can be identified in the lymph collected from an opening in the thoracic duct at the neck in from four to seven minutes after the injection.<sup>1</sup> The physiological importance of the lymph-movement is shown not only by the large amount of matter which daily leaves the lymphatic system to join the blood, but also by the evil effects which result from an undue accumulation of lymph, more or less changed in character, in the gaps of the tissues. Such an accumulation constitutes dropsy. It may occur in a serous cavity or in the subcutaneous tissue; in the latter case giving rise to a peculiar swelling which "pits on

<sup>1</sup> S. Tschirwinsky: "Zur Frage über die Schnelligkeit des Lymphstromes und der Lymphfiltration," *Centralblatt für Physiologie*, 1895, Band ix. S. 49.

pressure." Any tissue the meshes of which are thus engorged with lymph is said to be "œdematous."<sup>1</sup>

## PART II.—THE INNERVATION OF THE HEART.<sup>2</sup>

It has long been known that the frog's heart can be kept beating for many hours after its removal from the body. In 1881, Martin succeeded in maintaining the beat of the dog's heart after its complete isolation from the central nervous system and the systemic blood-vessels. Ludwig and his pupils have attained the same result in a different way. In 1895, Langendorff was able by circulating warmed oxygenated, defibrinated blood through the coronary vessels to maintain the hearts of rabbits, cats, and dogs in activity after their total extirpation from the body. Even pieces removed from the ventricle will contract for hours if fed with blood through a cannula in the branch of the coronary artery which supplies them.<sup>3</sup> It is evident, therefore, that the cause of the rhythmic beat of the heart lies within the heart itself, and not within the central nervous system.

**Cause of Rhythmic Beat.**—It has been much disputed whether the cardiac muscle possesses the power of rhythmical contraction or whether the rhythmic beat is due to the periodic stimulation of the muscle by the discharge of nerve-impulses from the ganglion-cells of the heart. The arrangement of the ganglion-cells and nerves suggests the latter view.

**The Intracardiac Ganglion-cells and Nerves.**—In the frog the cardiac nerves arise by a single branch from each vagus trunk and run along the great veins through the wall of the sinus venosus, where many ganglion-cells are found, to the auricular septum. Here they unite in a strong plexus richly provided with ganglion-cells. Two nerves of unequal length and thickness leave this plexus and pass along the borders of the septum to the auriculo-ventricular junction, where each enters a conspicuous mass of cells known as Bidder's ganglion. Ventricular nerves spring from these ganglia and can be followed with the unaided eye some distance on the ventricle. With the chloride-of-gold method, the methylene-blue stain, and especially the nitrate-of-silver impregnation, the ventricular nerves can be traced to their termination. Some difference of opinion exists regarding the manner of their distribution and the precise nature of their terminal organs. The following facts, however, may be considered established both for the batrachian and the mammalian heart.<sup>4</sup>

The ventricular nerves form a rich plexus beneath the pericardium and

<sup>1</sup> From *oîdema*, a swelling.

<sup>2</sup> The literature of the innervation of the heart and blood-vessels is now so large that only references to some of the principal investigations published since 1892 can be given here. For the titles of works prior to that date, the reader may consult Tigerstedt's *Lehrbuch der Physiologie des Kreislaufes*, 1893.

<sup>3</sup> Porter: *Journal of Experimental Medicine*, 1897, ii. p. 391.

<sup>4</sup> The literature of this subject has been collected by Heymans and Demoor: *Archives (Belge) de Biologie*, 1895, xiii. p. 619.



endocardium. Branches from these plexuses form a third plexus in the myocardium or heart muscle, from which arise a vast number of non-medullated terminal nerves, enveloping the muscle-fibres and ending in small enlargements or nodosities of various forms. Similar "varicose" enlargements are observed along the course of the nerves. The nerve-endings are in contact with the naked muscle-substance, the mode of termination resembling in general that observed in non-striated muscle. Ganglion-cells are found chiefly in the auricular septum and the auriculo-ventricular furrow, but are present also beneath the pericardium of the upper half of the ventricle. No ganglia have as yet been satisfactorily demonstrated within the apical half of the ventricle,<sup>1</sup> and most observers do not admit their presence within the ventricular muscle itself. The nerve-cells are unipolar, bipolar, or multipolar.

Certain unipolar cells in the frog are distinguished by a spherical form, a pericellular network, and two processes—namely, the axis-cylinder or straight process, and the spiral process. The latter is wound in spiral fashion about the axis-cylinder, ending in the pericellular net. According to Retzius and others, the spiral is not really a process of the cell, but arises in a distant extra-cardiac cell and carries to the heart-cell a nervous impulse which is transmitted from the spiral process to the cell by means of the contact between the pericellular net and the cell-body. Section of the cardiac fibres of the vagus causes the spiral "process" and pericellular net to degenerate, the cell-body and axis-cylinder process remaining untouched, showing that the spiral process is the terminal of a nerve-fibre running in the vagus trunk.<sup>2</sup>

*Nerve-theory of Heart-beat.*—The theory of the nervous origin of the heart-beat rests in part on the correspondence between the degree of contractility of the various parts of the heart and the number of nerve-cells present in them. Thus the power of rhythmical contraction is greater in the auricle, in which there are many cells, than in the ventricle, in which there are fewer. The properties of the apical half, or "apex," of the ventricle are considered to be of especial importance in the study of this problem, because the apex, as has been said, is believed to contain no ganglion-cells. This part of the ventricle stops beating when separated from the heart, while the auricles and the ventricular stump continue to beat. The apex need not be cut away in order to isolate it. By ligating or squeezing the frog's ventricle across the middle with a pair of forceps the tissues at the junction of the upper and the lower half of the ventricle can be crushed to the point at which physiological connection is destroyed but physical continuity still preserved. Such frogs have been kept alive as long as six weeks. The apex does not as a rule beat again. The exceptions can be explained as the consequence of accidental stimulation. The conclusion drawn is that the apex, in which ganglion-cells have not been satisfactorily demonstrated, has not the power of spontaneous pulsation which

<sup>1</sup> Schwartz: *Archiv für mikroskopische Anatomie*, 1899, liii. S. 63. Compare Dogiel: *Ibid.*, S. 237.

<sup>2</sup> Nikolajew: *Archiv für Physiologie*, 1893, Suppl. Bd., S. 73.



distinguishes the remainder of the heart. This view is further supported by the observation that a slight stimulus applied to the base of a resting ventricle will often provoke a series of contractions, while the same stimulus applied to the apex will cause but a single contraction.

Much may be hoped from comparative studies. In the medusæ, for example, the margin of the swimming bell, by the rhythmical contraction of which the animal is driven through the water, is provided with a double nerve-ring and ganglion-cells, while the centre contains only scattered and infrequent ganglion-cells. If the margin is separated from the centre and both are placed in sea-water, only the part containing many nerve-cells beats rhythmically. Loeb concludes that inasmuch as the whole medusa (*Gonionemus*) beats in sea-water in the rhythm of the margin, the failure of the isolated centre to beat in that medium can only be explained by the lack of nerve-cells.<sup>1</sup>

The fact that the normal contraction begins in the sinus, Howell explains by the greater sensitiveness of that part to chemical stimulation.<sup>2</sup>

The action of muscarin on the heart is often held to indicate the nervous origin of the heart-beat. Muscarin arrests the heart of the frog and other vertebrates, but has no similar action on any other muscle either striped or smooth, nor does it arrest the heart of insects and mollusks. It follows that muscarin does not cause arrest by acting directly upon the contractile material of the heart. The contractile material being excluded, the assumption of a nervous mechanism on the integrity of which the heart-beat depends seems necessary to explain the effect of the poison.

Further arguments are based on uncertain analogies between the heart and other rhythmically contracting organs.

*Muscular Theory of Heart-beat.*<sup>3</sup>—The evidence just stated cannot be regarded as proof of the nervous origin of the heart-beat. The most that can be claimed is that it makes such a conception plausible. The cause of the beat probably lies in the contractile substance rather than the nerve-cells. It is, at all events, certain that the cardiac muscle is capable of prolonged rhythmic contraction. It has been shown that a strip of muscle cut from the apex of the tortoise ventricle and suspended in a moist chamber begins in a few hours to beat apparently of its own accord with a regular but slow rhythm, which has been seen to continue as long as thirty hours. If the strip is cut into pieces and placed on moistened glass slides, each piece will contract rhythmically. Yet in the apex of the heart no nerve-cells have been found.

The apex of the batrachian heart will beat rhythmically in response to a constant stimulus. Thus if the apex is suspended in normal saline solution and a constant electrical current kept passing through it, beats will appear after a time, the frequency of pulsation increasing with the strength of the

<sup>1</sup> Loeb: *American Journal of Physiology*, 1900, iii. p. 383.

<sup>2</sup> Howell: *Ibid.*, ii. p. 47.

<sup>3</sup> A valuable bibliography is given by Engelmann: *Archiv für die gesammte Physiologie*, 1896, lxx. p. 109; see also *Ibid.*, p. 535.

current.<sup>1</sup> Very strong currents cause tonic contraction. An apex made inactive by Bernstein's crushing can be made to beat again by clamping the aorta and thus raising the endocardiac pressure. Chemical stimulation is also effective. Delphinin, quinine, muscarin with atropin, atropin alone, morphin and various other alkaloids, dilute mineral acids, dilute alkalies, bile, sodium chloride, alcohol, and other bodies,<sup>2</sup> when painted on the resting ventricle, call forth a longer or shorter series of beats. Stimulation with induction shocks gives a similar result.

Other muscles in which no nerve-cells have been discovered can contract rhythmically. Thus the bulbus aortæ of the frog beats regularly after its removal from the body, even the smallest pieces showing under the microscope rhythmical contractions. Engelmann, who observed this fact, declares that the entire bulbus is lacking in nerve-cells. This is contradicted by Dogiel; yet it seems hardly reasonable that these "smallest pieces" which Engelmann mentions were each provided with ganglion-cells. It is more probable that the contractions were the result of a constant artificial stimulus. Curarized striated muscles placed in certain saline solutions may contract from time to time. The hearts of many invertebrates in which ganglion-cells are apparently absent beat rhythmically.

Much has been made of the fact that the ganglion-cells grow into the heart long after the cardiac rhythm is established, showing that the embryonic heart muscle has rhythmic contractile powers. The adult heart muscle, it is alleged, retains certain embryonic peculiarities of structure, and as structure and function are correlated, should also retain the embryonic power of contraction without nerve-cells.

A positive demonstration that the nerve-cells in the heart are not essential to its contractions is secured by removing the tip of the ventricle of the dog's heart and supplying it with warm defibrinated blood through a cannula tied into its nutrient artery. Long-continued, rhythmical, spontaneous contractions are thus obtained.<sup>3</sup> As the part removed contains no nerve-cells, the observed contractions can only arise in the muscular tissue, provided we make the (at present) safe assumption that the nerve-fibres do not originate impulses capable of inducing rhythmic muscular contractions. The demonstration that the nerve-cells are not essential to contraction, places us one step nearer the true cause of contraction. It is some agency acting on the contractile substance. Evidence is accumulating that this agent is a chemical substance, or substances, brought to the contractile matter by the blood. For this chemical stimulation calcium is apparently essential, and for rhythmic contraction and relaxation Howell<sup>4</sup> finds a certain proportion of potassium

<sup>1</sup> Langendorff: *Archiv für die gesammte Physiologie*, 1895, lxi. p. 336.

<sup>2</sup> Kaiser: *Zeitschrift für Biologie*, 1895, xxxii. p. 6.

<sup>3</sup> Porter: *Journal of Experimental Medicine*, 1897, ii. p. 391.

<sup>4</sup> Howell: *American Journal of Physiology*, 1898, ii. p. 47; Loeb: *Ibid.*, 1900, iii. p. 394. The reader is recommended to examine these suggestive papers for himself.



also necessary. Sodium chloride must be present to preserve the osmotic equilibrium between contractile tissue and surrounding liquid. As phrased by Loeb, it may be assumed that the sodium, calcium, and potassium ions must exist in definite proportions in the tissue which is expected to show rhythmical activity. Only so long as these proportions are preserved does the tissue possess such physical properties and such labile equilibrium as to be capable of rhythmical processes or contractions.

**The Excitation-wave.**—The change in form which constitutes what commonly is called the cardiac contraction is preceded by a change in electrical potential, supposed to be a manifestation of the unknown process by which the heart-muscle is excited to contract. Both the contraction and the electrical change sweep over the heart in the form of waves, and it has become the custom to speak of the electrical change as the excitation-wave. It should not be forgotten, however, that this usage rests merely on an assumption, for the real nature of the excitation is still a mystery. The contraction-wave begins normally at the great veins, travels rapidly through the auricle, and, after a distinct interval, spreads through the ventricle. The excitation-wave, which precedes and is the cause of the contraction, probably takes the same course,<sup>1</sup> and in fact it is possible to show that the change in electrical potential actually begins under normal conditions at the great veins and passes thence over the entire heart. But this sequence is not invariable. The ventricle under abnormal conditions has been seen to contract before the auricle, the normal sequence of great veins, auricle, and ventricle being reversed.<sup>2</sup> The energy of the ventricular muscle-cell may, therefore, be discharged by an excitation arising within the ventricle itself. Evidence of this is afforded also by the experiment of Wooldridge, who isolated the ventricles by drawing a silk ligature tightly about the auricles at their junction with the ventricles, completely crushing the muscle and nerves of the auricle in the track of the ligature without tearing through the more resistant pericardium. This experiment was repeated the following year by Tigerstedt, who devised a special clamp for crushing the auricular tissues. Both observers found that the auricles and ventricles continued to beat. The rhythm, however, was no longer the same. The ventricular beat was slower than before and was independent of the beat of the auricle. Thus the ventricle, no longer connected physiologically with the auricle, develops a rhythm of its own, an idio-ventricular rhythm. It seems improbable that the very small part of the auricular tissue which cannot be included in Wooldridge's ligature for fear of closing the coronary arteries should be able to maintain the ventricular contractions.

Independent contraction is said to be secured by properly regulated excitation of the cardiac end of the cut vagus nerve. Stimuli of one second duration applied to the vagus at intervals of six to seven seconds arrest the auricles completely, but do not stop the ventricles, except during the second of stimulation. The ventricles, now dissociated from the auricles, beat with a rhythm

<sup>1</sup> Bottazzi: *Lo sperimentale*, 1898, li. No. 2.

<sup>2</sup> Recently studied by Engelmann: *Archiv für die gesammte Physiologie*, 1895, lxi. p. 275.



different from that which characterized the normal heart. The force of this demonstration is somewhat weakened by the possibility that the auricles, although not beating themselves, might still excite the ventricles to contraction.

*Conduction of the Excitation.*—If the points of non-polarizable electrodes are placed on the surface of the ventricle and connected with a delicate galvanometer, a variation of the galvanometer needle will be seen with each ventricular beat. If one electrode is placed near the base of the heart and the other near the apex it is seen that the former electrode becomes negative before the latter, indicating that the part of the heart muscle on which the basal electrode rests is stimulated before the apical portion, and that the difference in electrical potential, or excitation-wave, according to the prevailing hypothesis, travels as a wave over the ventricle from the base to the apex (see Fig. 27). Burdon-Sanderson and Page have found that the duration of the difference of potential is about two seconds in the frog's heart at ordinary temperatures. Cooling lengthens the period of negativity, warming diminishes it. Some observers believe that the excitation-wave under certain conditions returns toward the base after having reached the apex. The speed of the excitation-wave has been measured by the interval between the appearance of negative variation in the ventricle when the auricle is stimulated first near and then as far as possible



FIG. 27.—The electrical variation in the spontaneously contracting heart of the frog, recorded by a capillary electrometer, the apex being connected with the sulphuric acid and the base with the mercury of the electrometer. The changes in electrical potential are shown by the line *e, e*, which is obtained by throwing the shadow of the mercury in the capillary on a travelling sheet of sensitized paper. The contraction of the heart is recorded by the line *h, h*. Time, in  $\frac{1}{10}$  second, by *i, i*. The curves read from left to right. The electrical variation is biphasic: in the first phase the base is negative to the apex; in the second, the apex is negative to the base; the negative variation passes as a wave from base to apex (Waller, 1887, p. 231).

from the non-polarizable electrodes. The interval is the time which the excitation-wave requires to pass the distance between the two points stimulated. The average rate is at least 50 millimeters per second.<sup>1</sup> The negative variation begins apparently instantly after the application of the stimulus. Its phases and their characteristics have been described by Engelmann.

The latent period of a frog's heart muscle is about 0.08 second.

<sup>1</sup> Burdon-Sanderson and Page (*Journal of Physiology*, 1880, ii. p. 426) give 125 millimeters per second.

Although the normal course of the excitation-wave is from base to apex, it can be made to travel in any direction. If the frog's ventricle is cut with fine scissors into a number of pieces in such a way as to leave small bridges of heart-tissue between each piece, and any one of the pieces is stimulated, the contraction will begin in the stimulated piece and then run from piece to piece over the connecting bridges until all have successively contracted. The direction in which the excitation-wave travels can thus be altered at the pleasure of the operator.

Whether the excitation is propagated from muscle-cell to muscle-cell or by means of nerve-fibres has given rise to much discussion. Anatomical evidence can be adduced on both sides. On the one hand the rich plexus of nerve-fibres everywhere present in the heart-muscle suggests conduction through nerves; on the other is the intimate contact of neighboring muscle-cells over a part at least of their surface, thus bringing one mass of irritable protoplasm against another and offering a path by which the excitation might travel from cell to cell.

If the excitation-wave were conducted by means of nerves, the difference between the moment of contraction of the ventricle when the auricle is stimulated near the ventricle, and again as far as possible from the ventricle, should be very slight, because of the great speed at which the nervous impulse travels (about 33 meters per second). If, on the contrary, the conduction were by means of muscle, the difference would be relatively much greater, corresponding to the much slower conductivity of muscular tissue. It has been found by Engelmann that the ventricle contracts later when the auricle is stimulated far from the ventricle than when it is stimulated near the ventricle. The rate of propagation being calculated from the difference in the time of ventricular contraction was found to be 90 millimeters per second, which is about 300 times less than the rate which would have been obtained had conduction over the measured distance taken place through nerves.<sup>1</sup> Hence the stimulus that travels through the auricle to the ventricle and causes its contraction should be propagated in the auricle by muscle-fibres and not by nerves.

It is possible to cut the ventricular muscle in a zigzag or spiral fashion that makes probable the severance of all the nerve-fibres in the line of the cut, and yet the contraction will pass from one end to the other of the isolated strip.<sup>2</sup>

*Passage of Excitation-wave from Auricle to Ventricle.*—The normal contraction of the heart begins, as has been said, at the junction of the great veins and the auricle, spreads rapidly over the auricle and, after a distinct pause, reaches the ventricle. The normal excitation-wave preceding the contraction passes likewise from the auricle to the ventricle and is delayed at or

<sup>1</sup> Engelmann: *Archiv für die gesammte Physiologie*, 1896, lxii. p. 549.

<sup>2</sup> Porter: *American Journal of Physiology*, 1899, ii. p. 127. The co-ordination of the ventricles is discussed in this paper, and also by von Vintschgau: *Archiv für die gesammte Physiologie*, 1899, lxxvi. p. 59.



near the auriculo-ventricular junction. The controversy over the nervous or muscular conduction of the excitation within the auricle and ventricle has been extended to its passage from auricle to ventricle. A path for conduction by nerves is presented by the numerous nerves which go from the auricle to the ventricle. It has been shown recently that muscular connections also exist. In the frog, muscle-bundles pass from the auricle to the ventricle where the auricular septum adjoins the base of the ventricle. Muscular bridges pass also from the sinus venosus to the auricles and from the ventricle to the bulbus arteriosus.<sup>1</sup> These muscle-fibres appear to be in intimate contact with the muscle-cells of the divisions of the heart which they unite. Gaskell believes that the connecting fibres are morphologically and physiologically related to embryonic muscle, and therefore possess the power of contracting rhythmically.

The delay experienced by the excitation in its passage from the auricle to the ventricle—in other words, the normal interval between the contraction of the auricle and the contraction of the ventricle—is explained by those favoring the nervous conduction as the delay which the excitation experiences in discharging the ganglion-cells of the ventricle, in accordance with the well-known hypotheses of the retardation of the nerve-impulse in sympathetic ganglia and the slow passage of the nervous impulse through spinal cells.

The explanation given by those who believe in muscular conduction is that the small number of muscular fibres composing the bridge between auricle and ventricle acts as a "block" to the excitation-wave. If the auricle of the tortoise heart is cut into two pieces connected by a small bridge of auricular tissue, the stimulation of one piece will be followed immediately by the contraction of that piece, and after an interval by the contraction of the other. The smaller the bridge, the longer the interval; that is the longer the excitation-wave will be in passing from one piece to another.

The duration of the pause or "block" in the frog has been found to be from 0.15 to 0.30 second. The length of the muscle-fibres connecting auricle and ventricle is about one millimeter. The speed of the excitation-wave in embryonic heart muscle is from 3.6 to 11.5 millimeters per second. The duration of the pause agrees, therefore, with the time which would be required for muscular conduction.<sup>2</sup>

The extensive extirpations of the auricular nerves which have been made without stopping conduction from auricle to ventricle<sup>3</sup>—for example, the extirpation of the entire auricular septum of the frog's heart—are of little importance to this question, since the great number of nerve-cells revealed by recent methods make it improbable that any extirpation short of total removal of both auricles could cut off all the nerve-cells of the auricle.

It is possible to explain the occurrence of intermittent or irregular con-

<sup>1</sup> Engelmann: *Archiv für die gesammte Physiologie*, 1894, lvi. p. 158.

<sup>2</sup> Engelmann: *Ibid.*, p. 159.

<sup>3</sup> Hofmann: *Ibid.*, 1895, lx. p. 169.



tractions by alterations in the conductivity or irritability of the several parts of the heart successively traversed by the excitation wave. For example, a lessening of the normal conductivity at the auriculo-ventricular junction might permit only every second sino-auricular impulse to reach the ventricle; in this case the ventricle would drop every second beat. The same intermittence would result if the irritability of the ventricle were so far reduced that it could not respond to the normal excitation.<sup>1</sup> Engelmann has recently found that ventricular systole lowers the conductivity of the ventricle for a time.<sup>2</sup>

**Refractory Period and Compensatory Pause.**—Schiff found in 1850 that the heart which contracted to each stimulus of a series of slowly repeated mechanical stimuli would not contract to the same stimuli if they followed each other in too rapid succession. Kronecker got a similar result with induction shocks. The heart contracted to every stimulus only when the interval between them was not too brief. The following year Marey published a systematic study of the phenomenon. He observed that the irritability of the heart sank during a part of the systole, but returned during the remainder of the systole and the following diastole. The stimulus which fell between the beginning of the systole and its maximum produced no extra contraction, whilst that which fell between the maximum of one systole and the beginning of the next called forth an extra contraction. During a part of the cardiac cycle therefore the heart is "refractory" toward stimuli. The irritability of the heart is removed for a time by an adequate stimulus.

Kronecker and Marey noticed further that stimulation with the induction shock during the non-refractory period did not influence the total number of systoles. The extra systole called forth by the artificial stimulus was followed by a pause the length of which was that of the normal pause plus the interval between the appearance of the extra systole and what would have been the end of the cardiac cycle in which the extra systole fell. The extra length of this pause restored the normal frequency or rhythm. It was called the compensatory pause (see Fig. 28).<sup>3</sup>

The systole following the extra contraction and its compensatory pause is of marked strength, at least in the surviving mammalian heart (cat). The weaker the extra systole the stronger the first subsequent contraction. The unusual force of this "compensatory systole" may serve to compensate the loss in the output of the heart incident to the disturbance in its rhythm.<sup>4</sup>

If the heart, or the isolated apex, is beating at a rate so slow that an extra contraction falling in the interval between two normal contractions has time to complete its entire phase before the next normal contraction is due, there will be no compensatory pause.<sup>5</sup>

<sup>1</sup> Oehrwall: *Skandinavisches Archiv für Physiologie*, 1898, viii. p. 1.

<sup>2</sup> Engelmann: *Archiv für die gesammte Physiologie*, 1896, lxii. p. 543.

<sup>3</sup> Courade: *Archives de Physiologie*, 1897, p. 69.

<sup>4</sup> Langendorff: *Archiv für die gesammte Physiologie*, 1898, lxx. p. 473.

<sup>5</sup> Kaiser: *Zeitschrift für Biologie*, 1895, xxxii. p. 449.

The refractory phase disappears with sufficiently strong stimuli, especially if the heart is warmed. In such a case an artificial stimulus falling in the beginning of a spontaneous contraction produces an extra contraction. This extra contraction, however, comes first after the end of the systole during which the artificial stimulation is made, occurring in fact toward the end of the



FIG. 28.—The refractory period and compensatory pause. The curves are recorded by a writing lever resting on the ventricle of the frog's heart. They read from left to right. A break in the horizontal line below each curve indicates the moment at which an induction shock was sent through the ventricle. In curves 1, 2, and 3 the ventricle proved refractory to this stimulus; in the remaining curves, the stimulus having fallen outside the refractory period, an extra contraction and compensatory pause are seen. Many of the phenomena mentioned in the text are illustrated by this figure (Marey, 1876, p. 72).

following diastole. The latent period of such a contraction lengthens with the length of the interval between the artificial stimulation and the end of the systole.

A refractory period has been demonstrated in the auricle of the frog<sup>1</sup> and dog;<sup>2</sup> in the ventricle of the cat, rabbit, and dog, and in the sinus venosus and bulbus arteriosus of the frog. It is said not to be present in the lobster.<sup>3</sup>

<sup>1</sup> Engelmann: *Archiv für die gesammte Physiologie*, 1894, lix. p. 322.

<sup>2</sup> Meyer: *Archives de Physiologie*, 1893, p. 185; Cushny and Matthews: *Journal of Physiology*, 1897, xxi. p. 213.

<sup>3</sup> Hunt, Bookman, and Tierney: *Centralblatt für Physiologie*, 1897, xi. p. 276.



In some cases, the extra stimulus provokes not merely one, but two or three extra contractions.

The amplitude of the extra contraction increases with the length of the interval between the maximum of contraction and the extra stimulus. If the extra stimulus is given at the beginning of relaxation, the extra contraction is exceedingly small; on the other hand, the extra contraction may be greater than the primary one, when the stimulus falls in the pause between two normal beats.

The supplementary systole of the auricle is sometimes followed by a supplementary systole and compensatory pause of the ventricle, sometimes by the compensatory pause alone, probably because the excitation wave reaches the ventricle during its refractory period. Multiple extra contractions of the auricle are often followed by the same number of extra contractions of the ventricle. If the frog's heart is made to beat in reversed order, ventricle first, auricle second, extra contractions of the ventricle may be produced, and will cause extra contractions of the auricle with compensatory pause. If the reversed excitation wave travelling from the ventricle to the auricle reaches the latter during auricular systole, the extra auricular contraction is omitted, but a distinct though shortened compensatory pause is still observed. The phenomena with reversed contraction are therefore similar to those seen under the usual conditions.<sup>1</sup>

Kaiser finds in frogs poisoned with muscarin that stimulation of the ventricle during the refractory period causes the contraction in which the stimulus falls to be more complete, as shown by the contraction curve rising above its former level. He concludes that the ventricle is not wholly inexcitable even during the refractory period.

The question whether the refractory state and compensatory pause are properties of the muscle-substance or of the nervous system of the heart has excited considerable attention. If the ganglion-free apex of the frog's ventricle is stimulated by rapidly repeated induction shocks it can be made to contract periodically for a time. By momentarily increasing the strength of any one induction shock an extra stimulus can be given from time to time. When the extra stimulus falls after the contraction maximum or during diastole an extra contraction results, otherwise not. The refractory period exists, therefore, independently of the cardiac ganglia.

The compensatory pause can also, though not always, be secured with the ganglion-free apex.<sup>2</sup>

The refractory period has been used to show how a continuous stimulus might produce a rhythmic heart-beat. The continuous stimulus cannot affect the heart during the refractory period from the beginning to near the maximum of systole. At the close of the refractory period the constant stimulus

<sup>1</sup> Kaiser: *Zeitschrift für Biologie*, 1895, xxxii. p. 19.

<sup>2</sup> Kaiser: *Ibid.*, p. 449; for experiments on the embryo, see Pickering: *Journal of Physiology*, 1896, xx. p. 165.



becomes effective, causing an extra contraction with long latent period. This latent period is, according to this theory, the interval between the first and the second contraction.

A tonic contraction<sup>1</sup> of the heart muscle is sometimes produced by strong, rapidly repeated induction shocks and by various other means, such as filling the ventricle with old blood, by weak sodium hydrate solution, and by certain poisons, such as digitalin and veratrin.

#### A. THE CARDIAC NERVES.

The cardiac nerves are branches of the vagus and the sympathetic nerves.

In the *dog* the vagus arises by about a dozen fine roots from the ventrolateral aspect of the medulla and passes outward to the jugular foramen in company with the spinal accessory nerve. In the jugular canal the vagus bears a ganglion called the jugular ganglion. The spinal accessory nerve joins the vagus here, the spinal portion almost immediately leaving the vagus to be distributed to certain muscles in the neck, while the medullary portion passes to the heart through the trunk ganglion and thereafter in the substance of the vagus. Directly after emerging from the skull, the vagus presents a second ganglion, fusiform in shape and in a fairly large dog about one centimeter in length. From the caudal end or middle of this "ganglion of the trunk" is given off the superior laryngeal nerve, slightly behind which a large nerve is seen passing from the sympathetic chain to the trunk of the vagus. This nerve is in reality the main cord of the sympathetic chain, the sympathetic nerve being bound up with the vagus from the "inferior" cervical ganglion to the point just mentioned. Posterior to the trunk ganglion of the vagus, the vago-sympathetic runs caudalward as a large nerve dorsal to the common carotid artery as far as the first rib or near it, where it enters the so-called inferior cervical ganglion. This ganglion belongs to the sympathetic system and not to the vagus; from a morphological point of view it is the middle cervical sympathetic ganglion. The true inferior cervical sympathetic ganglion is fused with the first one or two thoracic ganglia to form the ganglion stellatum, situated opposite the first intercostal space. At the "inferior cervical" ganglion the vagus and the sympathetic part company, the vagus passing caudalward behind the root of the lung and the sympathetic passing to the stellate ganglion, dividing on its way into two portions (the annulus of Vieussens), which embrace the subclavian artery. In many cases the lower loop of the annulus of Vieussens joins the trunk of the vagus caudal to the ganglion.

The cardiac nerves spring from the vagus and the sympathetic nerve in the region of the inferior cervical ganglion. They may be divided into an inner and an outer group.

The inner group is composed of one medium, one thick, and two or three slender nerves. The nerve of medium thickness springs from the gan-

<sup>1</sup> Hunt, Bookman, and Tierney: *Centralblatt für Physiologie*, 1897, xi. p. 274.

gion itself. The thick branch rises from the trunk of the vagus near the origin of the inferior laryngeal nerve about 1.25 centimeters caudal to the

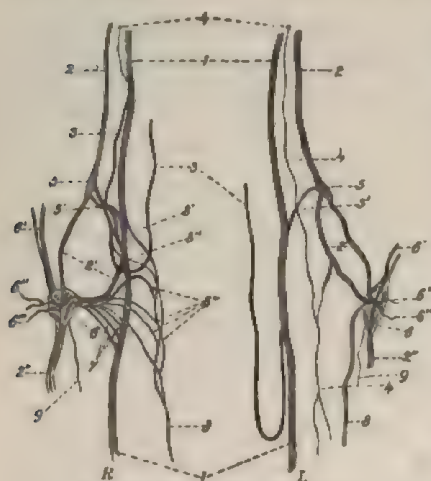


FIG. 29.—Cardiac plexus and stellate ganglion of the cat, drawn from nature after the removal of the arteries and veins; about one and one-half times natural size (Boehm, 1875, p. 258):

R, right; L, left: 1, 1, vagus nerve; 2, cervical sympathetic; 2', annulus of Vieussens; 2'', thoracic sympathetic; 3, recurrent laryngeal nerve; 4, depressor nerve, entering the vagus on the right, on the left running a separate course to the heart; 5, middle (often called "inferior") cervical ganglion; 5', communicating branch between middle cervical ganglion and vagus nerve; 6, stellate ganglion; 6', 6'', spinal roots of stellate ganglion; 7, communication between stellate ganglion and vagus; 8, 8'', cardiac nerves.

here given can be regarded as a close approximation only, so frequent are the individual variations.<sup>1</sup>

In the *rabbit* the cervical sympathetic and the vagus trunk are not joined, as in the dog, but run a separate course. Cardiac fibres from the spinal cord reach the lower cervical and first thoracic ganglion (ganglion stellatum) along their rami communicantes and pass to the heart by two sympathetic cardiac nerves, one from the inferior cervical ganglion and one from the ganglion stellatum.

The arrangement of the cardiac nerves in the *cat* is shown in Figure 29.

In the *frog* the cardiac nerves, both vagal and sympathetic, reach the heart through the splanchnic branch of the vagus. The sympathetic fibres pass out of the spinal cord with the third spinal nerve, through the ramus communicans of this nerve into the third sympathetic ganglion,<sup>2</sup> up the sympathetic chain to the ganglion of the vagus, and down the vagus trunk to the heart.

<sup>1</sup> Details concerning the composition of the cardiac plexuses in the dog are given by Lim Boon Keng: *Journal of Physiology*, 1893, xiv. p. 467.

<sup>2</sup> It is probable that the fibres of spinal origin end in the sympathetic ganglia, making contact there with sympathetic ganglion-cells, the axis-cylinder processes of which pass up the cervical chain and descend to the heart in company with the vagus.

inferior cervical ganglion. It can be easily followed to its final distribution. It passes behind the vena cava superior, perforates the pericardium, and runs parallel with the ascending aorta across the pulmonary artery, on which it lies in the connective tissue already divided into two or three tolerably thick twigs or spread in a fan of smaller branches. These now bend beneath the artery, pass round its base on the inner side, and reach the anterior inter-ventricular groove. Here they spread over the surface of the ventricle. The slender branches leave the vagus trunk caudal to the branch just described.

The outer group comprises two thick branches—namely, an upper nerve, springing from the ganglion or from the trunk of the vagus near it, and a lower nerve, from the lower loop of the annulus, or from the vagus 1–1½ centimeters lower down. Each of these thick branches may be replaced by a bundle of finer branches, and in fact the description of the cardiac nerves



The connection of the extrinsic cardiac nerves with the intracardiac muscle and nerve-cells is not yet determined satisfactorily. Certain fibres in the vagus, said to be derived from the spinal accessory nerve, terminate in "end-baskets" embracing sympathetic ganglion-cells, the axis-cylinder processes of which end on the cardiac muscle-fibres. Probably the inhibitory action of the vagus is exercised through these cells, as it is lost in animals poisoned with nicotine, which is known to paralyze, in other situations, either the end-baskets about sympathetic cells or the body of the cell itself. Other vagus fibres apparently terminate (or arise) in an end-brush in the pericardium and endocardium.

The augmentor apparatus consists of two, possibly three, neurons. The cell-body of one lies in the spinal cord; its axis-cylinder process leaves the cord in the white ramus and terminates in a ganglion of the sympathetic chain (inferior cervical, stellate ganglion). The axis-cylinder process of the sympathetic ganglion-cell passes directly to the cardiac muscle-fibre on which it ends, or, possibly, terminates in physiological contact with the dendrites of a third neuron lying in the heart, the neuraxon of which carries the augmenting impulse to the muscle-cell. Stimulation of the white ramus causes augmentor effects. In nicotine-poisoning, these effects cannot be obtained; but stimulation on the distal side—the cardiac side—of the cell-body about which the neuraxon ends, still causes augmentation. If nicotine paralyzes the sympathetic cell-body, this experiment proves that there is no cell in this neuron chain between the point stimulated and the muscle-fibre; if it paralyzes the end-basket and not the cell-body, the existence of the third (intracardiac) neuron in the chain is possible, provided the communication between the second and the third neuron is not by means of an end-basket; but, as Dogiel and Huber assume, by a contact with the dendrites, similar to that observed by them in other sympathetic cells, and not sensitive to nicotine.

#### THE INHIBITORY NERVES.

In 1845, Ernst Heinrich and Eduard Weber announced that stimulation of the vagus nerves or the parts of the brain where they arise slows the heart even to arrest. When one pole of an induction apparatus was placed in the nasal cavity of a frog and the other on the spinal cord at the fourth or fifth vertebra, the heart was completely arrested after one or two pulsations and remained motionless several seconds after the interruption of the current. During the arrest, the heart was relaxed and filled gradually with blood. When the stimulus was continued many seconds, the heart began to beat again, at first weakly and with long intervals, then more strongly and frequently, until at length the beats were as vigorous and as frequent as before, though all this time the stimulation was uninterrupted.

In order to determine from what part of the brain this influence proceeds, the electrodes were brought very near together and placed upon the cerebral hemispheres. The movements of the heart were not affected. Negative results followed also the stimulation of the spinal cord. Not until the medulla oblon-



gata between the corpora quadrigemina and the lower end of the calamus scriptorius was stimulated did the arrest take place. Cutting away the spinal cord and the remainder of the brain did not alter the result.

Having determined that the inhibitory power had its seat in the medulla oblongata, the question arose through what nerve the inhibitory influence is transmitted to the heart. In a frog in which the stimulation of the medulla had stopped the heart, the vagus nerves were cut and the ends in connection with the heart stimulated. The heart was arrested as before.

Thus the fundamental fact of the inhibition of a peripheral motor mechanism by the central nervous system through the agency of special inhibitory



FIG. 30.—Pulsations of frog's heart, inhibited by the excitation of the left vagus nerve (Tarchanoff, 1876, p. 296): C, pulsations of heart; S, electric signal which vibrated during the passage of the stimulating current, one vibration for each induction shock.

nerves was firmly established. A great number of investigations have demonstrated that this inhibitory power is found in many if not all vertebrates and not a few invertebrates.

The effect of vagus stimulation on the heart is not immediate; a *latent period* is seen extending over one beat and sometimes two, according to the moment of stimulation (see Fig. 30).

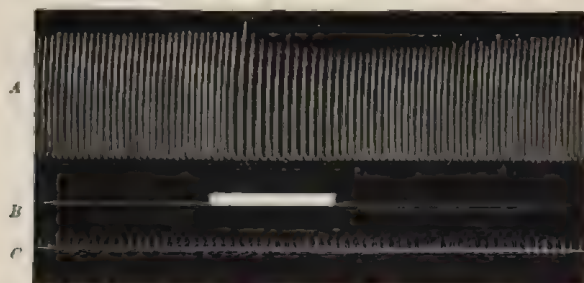


FIG. 31.—Showing the lengthened diastole and diminished force of ventricular contraction during weak stimulation of the peripheral end of the cut vagus nerve. The heart (cat) was isolated from both systemic and pulmonary vessels, and was kept beating by circulating defibrinated blood through the coronary arteries. A, Pressure in left ventricle which was filled with normal saline solution, and communicated with a Hürthle membrane manometer by means of a cannula which was passed through the auricular appendix and the mitral orifice; B, line drawn by the armature of an electro-magnet in the primary circuit; the heavy line indicates the duration of stimulation; C, time in seconds.

**Changes in the Ventricle.**—The *periodicity* of the ventricular contraction is altered by vagus excitation, a weak excitation lengthening the duration of diastole, while leaving the duration of systole unchanged (see Fig. 31). A stronger excitation, capable of modifying largely the force of the contraction, lengthens both systole and diastole.<sup>1</sup> The difficulty of producing a continued

<sup>1</sup> Meyer: *Archives de Physiologie*, 1894, p. 698; Arloing: *Ibid.*, p. 88.

arrest in diastole is much greater in some animals than in others. Even when easily produced, the arrest soon gives away in the manner described by E. H. and E. Weber, the heart beginning to beat in spite of the vagus excitation.<sup>1</sup>

The *force of the contraction*, measured by the height of the up-stroke of the intra-ventricular pressure curve, or by placing a recording lever on the heart, is lessened, this diminution in force appearing often before any noticeable change in periodicity.

The *diastolic pressure* increases, as is shown by the lower level of the curve gradually rising farther and farther above the atmospheric pressure line.

The *volume of blood* in the ventricle at the close of diastole is increased. So also is the volume at the close of systole (residual blood)—sometimes to such a degree that the volume of the heart at the end of systole may be greater than the volume of the organ at the end of diastole before the vagus was excited.

The *output and the input* of the ventricle, that is, the quantity of blood discharged and received, are both diminished by vagus excitation.

The *ventricular tonus*, or state of constant slight contraction on which the systolic contractions are superimposed, is also diminished, as is well shown by an experiment of Stefani.<sup>2</sup> In this experiment the pericardial sac is filled with normal saline solution under a pressure just sufficient to prevent the expansion of the heart in diastole. On stimulation of the vagus, the heart dilates further. A considerably higher pressure is necessary to overcome this dilatation. Stefani finds also that the pressure necessary to prevent diastolic expansion is much greater with intact than with cut vagi. Furthermore, the heart is much more easily distended by the rise of arterial pressure through compression of the aorta when the vagi are severed than when they are intact. Franck has noticed that the walls of the empty ventricle become softer when the vagus is stimulated.<sup>3</sup>

The *propagation of the cardiac excitation* is more difficult during vagus excitation. Bayliss and Starling demonstrate this on mammalian hearts made to contract by exciting the auricle three or four times per second; the ventricle as a rule responds regularly to every auricular beat. If, then, the vagus is stimulated with a weak induced current, the ventricle may drop every other beat, or may for a short time cease to respond at all to the auricular contractions. The defective propagation is not due to changes in the auricular contraction, for even an almost inappreciable beat of the auricle can cause the ventricle to contract. Nor is it due to lowered excitability of the ventricle, for the effect described is seen with currents too weak to depress the irritability of the ventricle to an appreciable extent.

The *sino-auricular and auriculo-ventricular contraction intervals* are usually lengthened by vagus excitation; sometimes, however, they are dimin-

<sup>1</sup> Hough: *Journal of Physiology*, 1895, xviii. p. 161. The terrapin heart is said not to escape, as a rule, from vagus inhibition.

<sup>2</sup> Compare Stefani: *Archives italiennes de Biologie*, 1895, xxiii. p. 175.

<sup>3</sup> See also Fischel: *Archiv für experimentelle Pathologie und Pharmacologie*, 1897, xxxviii. p. 228.



ished; the one may be increased, while the other is diminished. The vagus effect quickly reaches a maximum and then slowly decreases. The interval between the contractions of different parts of the sinus is sometimes increased by vagus excitation, so that the different parts are dissociated and beat at measurably different times. Attempts have been made to explain the several actions of the vagus nerve, together with the various forms of intermittent and irregular pulse, by variations in the transmission of the cardiac excitation;<sup>1</sup> but it is probable that alterations in the condition of the muscle-cells in the sinus, auricle, and ventricle are of equal or greater importance.<sup>2</sup>

The action of the vagus is accompanied by an *electrical variation*. This has been shown in the muscular tissue of the resting auricle of the tortoise (see Fig. 32). The auricle is cut away from the sinus without injuring the coronary nerve, which in the tortoise passes from the sinus to the auricle and contains the cardiac fibres of the vagus. After this operation the auricle and ventricle remain motionless for a time, and this quiescent period is utilized for the experiment. The tip of the auricle is injured by immersion in hot water, and the demarcation current (the injured tissue being negative toward the uninjured) is led off to a galvanometer. On exciting the vagus in the neck, the demarcation current is markedly increased. No visible change of form is seen in the auricular strip.

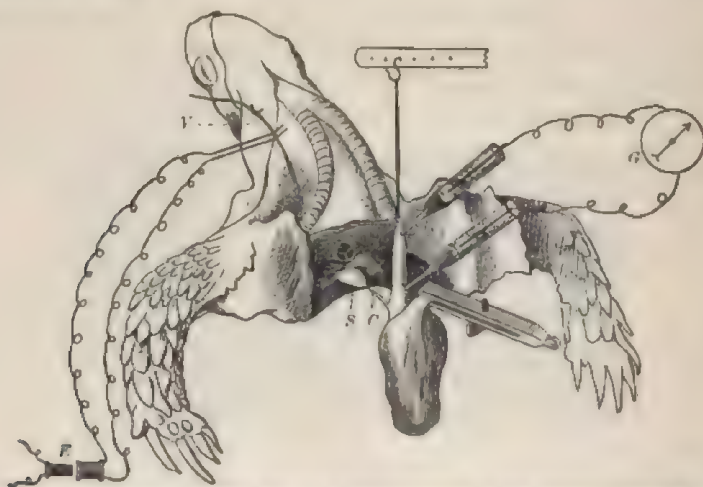


FIG. 32.—The tortoise heart prepared for the demonstration of the electrical change in the cardiac muscle accompanying the excitation of the vagus nerve: V, vagus nerve; C, coronary nerve; S, sinus and part of auricle in connection with it; G, galvanometer, in the circuit formed by two non-polarizable electrodes and the part of the auricle between them; E, induction coil (Gaskell, 1887).

**Changes in the Sinus and Auricle.**—There is little probability that the action of the vagus on the sinus and auricle, or great veins,<sup>3</sup> differs essentially from the action on the ventricle. The force of the contraction is diminished.

<sup>1</sup> Musken: *American Journal of Physiology*, 1898, i. p. 486.

<sup>2</sup> Holmann: *Archiv für die gesammte Physiologie*, 1898, lxxii. p. 409.

<sup>3</sup> Knoll: *Archiv für die gesammte Physiologie*, 1897, lxxiii. p. 339; Engelmann: *Ibid.*, 1896, lxx. p. 109.



The diastole is lengthened. The change in force appears earlier than the change in periodicity, and sometimes without it. On the whole, the sinus and auricle are more easily affected by vagus excitation than the ventricle.

**Action on Bulbus Arteriosus.**—If the bulbus arteriosus of the frog's heart is extirpated in such a way as to leave untouched the nerve-fibres that connect it with the auricular septum, the contractions of the isolated bulbus will be arrested when the peripheral end of the vagus is excited.<sup>1</sup>

**Diminished Irritability of Heart.**—During vagus excitation with currents of moderate strength, the arrested heart will respond to direct stimulation by a single contraction. With strong vagus excitation, however, the directly stimulated heart contracts not at all or less readily than before.

**Effects of Varying the Stimulus.**—A single excitation of the vagus does not stop the heart. Morat has investigated the effect of excitations of varied duration, number, and frequency on the tortoise heart.<sup>2</sup> With excitations of the same duration, the effect was minimal at 2 per second, maximal at 7 per second, diminishing thereafter as the frequency increased. The longer the stimulation, the longer (within limits) was the inhibition. An excitation that is too feeble or too slow, or, on the contrary, is over-strong or over-frequent, has no effect. Within limits, however, the degree of inhibition increases with the strength of the stimulus.

Weak stimuli affect primarily the auricles, diminishing frequency and force of contraction, and secondarily lower the frequency of the ventricle. Stronger stimuli arrest the auricle, the ventricles continuing to beat with almost undiminished force but with altered rhythm. Still stronger stimuli inhibit the ventricles also.

The frequency can be kept comparatively small by continued moderate stimulation.

**Arrest in Systole.**—The excitation of the tortoise vagus in the upper or middle cervical region is sometimes followed, according to Rouget,<sup>3</sup> by a state of continued, prolonged contraction—in short, an arrest in systole. The same effect is observed in rabbits strongly curarized and in curarized frogs. Arloing<sup>4</sup> noticed that the mechanical irritation produced by raising on a thread the left vagus nerve of a horse caused the right ventricle to remain contracted during seven seconds. The ventricular curve during this time presented the characters of the tetanus curve of a skeletal muscle. Recent observations by Frank,<sup>5</sup> Hunt,<sup>6</sup> Walther,<sup>7</sup> and others make it probable that a kind of summation and superposition of contractions may at times take place in the heart as in ordinary striated muscular tissue.

<sup>1</sup> Dogiel: *Centralblatt für die medizinischen Wissenschaften*, 1894, p. 227.

<sup>2</sup> Morat: *Archives de Physiologie*, 1894, p. 10.

<sup>3</sup> Rouget: *Ibid.*, p. 398.

<sup>4</sup> Arloing: *Ibid.*, 1893, p. 112.

<sup>5</sup> Frank: *Zeitschrift für Biologie*, 1899, xxxviii.

<sup>6</sup> Hunt, Bookman, and Tierney: *Centralblatt für Physiologie*, 1897, xi. p. 274.

<sup>7</sup> Walther: *Archiv für die gesammte Physiologie*, 1900, lxxviii p. 597.

**Comparative Inhibitory Power.**—One vagus often possesses more inhibitory power than the other.<sup>1</sup>

**Septal Nerves in Frog.**—The electrical stimulation of the peripheral stump of either of two large nerves of the inter-auricular septum in the frog alters the tonus and the force of contraction of the ventricle, but not the frequency. After section of these nerves, the excitation of the vagus has very little effect on the tonus, and almost none on the force of the ventricular beat, while the frequency is diminished in the characteristic manner. Evidently, therefore, the two large septal nerves take no part in the regulation of frequency, but leave this to the nerves diffusely distributed through the auricles. There is then an anatomical division of the septal branches of the frog's vagus, the fibres affecting periodicity running outside the septal nerves, while those modifying the force of contraction and the tonus of the ventricle run within them.<sup>2</sup>

**Nature of Vagus Influence on Heart.**—The nature of the terminal apparatus by which the vagus inhibits the heart is unknown. It is probable that the same intracardiac apparatus serves for both nerves, for Hüfler finds that when the heart escapes from the inhibition caused by continued stimulation of one vagus, the prolonged diastole growing shorter again, the immediate stimulation of the second vagus has no effect upon the heart.<sup>3</sup> Dogiel and Grahe have recently observed that the lengthening of diastole which follows stimulation of the peripheral stump of the vagus, the other vagus being intact, is less marked than when both vagi are cut.<sup>4</sup>

The earlier attempts to form a satisfactory theory for the inhibitory power of the vagus met with little success. The statement of the Webers' that the vagus inhibits the movements of the heart gave to nerves a new attribute, but is hardly an explanation. The view of Budge and Schiff, that the vagus is the motor nerve of the heart and that inhibition is the expression of its exhaustion, is now of only historical interest. Nor has a better fate overtaken the theory of Brown-Séquard, who saw in the vagus the vaso-motor nerve of the heart, the stimulation of which, by narrowing the coronary arteries, deprived the heart of the blood that, according to Brown-Séquard, is the exciting cause of the contraction.

Of recent years, the explanation that has commanded most attention is the one advanced by Stefani<sup>5</sup> and Gaskell, namely, that the vagus is the trophic nerve of the heart, producing a dis-assimilation or katabolism in systole and an assimilation or anabolism in diastole. Gaskell supports this theory by the observation that the after-effect of vagus excitation is to strengthen the force of the cardiac contraction and to increase the speed with which the excitation

<sup>1</sup> Hofmann: *Archiv für die gesammte Physiologie*, 1895, lx. p. 169.

<sup>2</sup> For other unusual alterations in the heart-beat in consequence of vagus excitation see Arloing: *Archives de Physiologie*, 1894, p. 163; and Knoll: *Archiv für die gesammte Physiologie*, 1897, lxvii. p. 587.

<sup>3</sup> Hough: *Journal of Physiology*, 1895, xviii. p. 198.

<sup>4</sup> Dogiel and Grahe: *Archiv für Physiologie*, 1895, p. 393. Changes in the peripheral efficiency of the vagi are discussed by McWilliams: *Proceedings Royal Society*, 1893, liii. p. 475.

<sup>5</sup> Stefani. *Archives italiennes de Biologie*, 1895, xxiii. p. 176.



wave passes over the heart, while the contrary effects are witnessed after the excitation of the augmentor nerves.

Various attempts have been made to prove a trophic action of the vagus on the heart by cutting the nerve in animals kept alive until degenerative changes in the heart-muscle should have had time to appear. The important distribution of the vagus nerve to many organs, and the consequently wide extent of the loss of function following its section, makes it difficult to decide whether the changes produced in the heart are not secondary to the alterations in other tissues. The work of Fantino will serve for an example of these investigations. Fantino cut a single vagus to avoid the paralysis of deglutition and the inanition and occasional broncho-pneumonia that follow section of both nerves. Young and perfectly healthy rabbits and guinea-pigs were selected. The operation was strictly aseptic, and all cases in which the wound suppurated were excluded. A piece of the nerve about one centimeter long was cut out, so that no reunion could be possible. After the operation the animals were as a rule lively, ate well, and gained weight. Post-mortem examination of animals killed two days or more after section of the vagus nerve disclosed no pathological changes in the lungs, spleen, liver, and stomach. In the heart, areas were found in which the nuclei and the striation of the muscle-cells had disappeared. Eighteen days after section the atrophy of the cardiac muscle in these areas was observed to be extreme. The degenerations following section of the right vagus were situated in a different part of the ventricular wall from those following section of the left nerve.

The effects of stimulation of the *vagus nerve in the new-born* do not differ essentially from those seen in the adult.<sup>1</sup>

The relation between the action of the *vagus* and the intracardiac pressure has been recently studied by Stewart. He finds that an increase in the pressure in the sinus or auricle makes it difficult to inhibit the heart through the vagus.

The inhibitory action of the vagus diminishes as the *temperature* of the heart falls. At a low limit the inhibitory power is lost, but may return when the heart is warmed again. Even when the stimulation of the trunk of the nerve has failed to affect the cooled heart, the direct stimulation of the sinus can still cause distinct inhibition. The power of inhibiting the ventricle is first lost. Loss of inhibitory power does not follow the raising of the heart to high temperatures. The vagus remains active to the verge of heart arrest, and resumes its power as soon as the temperature is lowered.

#### THE AUGMENTOR NERVES.

v. Bezold observed in 1862 that stimulation of the cervical spinal cord caused an increased frequency of heart-beat. This seemed to him to prove the existence of special accelerating nerves. Ludwig and Thiry, however, soon pointed out that stimulation of the spinal cord in the cervical region excited many vaso-constrictor fibres, leading to the narrowing of many vessels and a corresponding rise of blood-pressure. The acceleration of the heart-beat

<sup>1</sup> Meyer. *Archives de Physiologie*, 1893, p. 477.



accompanying this rise in blood-pressure would alone explain the observation of von Bezold. Three years later Bever and von Bezold were more successful. The influence of the vaso-motor nerves was excluded by section of the spinal cord between the first and second thoracic vertebrae. Stimulation of the cervical cord now caused an increase in the frequency of the heart-beat without a simultaneous increase of blood-pressure. The fibres carrying the accelerating impulse were traced from the spinal cord to the last cervical ganglion and from there toward the heart.

In the *dog* the "augmenting" or "accelerating" nerves thus discovered leave the spinal cord mainly by the roots of the second dorsal nerves, and enter the ganglion stellatum, whence they pass through the anterior and posterior loops of the annulus of Vieussens into the inferior cervical ganglion, from which they go, in the cardiac branches of the latter, to the heart. Some of the cardiac fibres in the annulus pass directly thence to the cardiac plexus and do not enter the inferior cervical ganglion.

In the *rabbit*, the course of the augmentor fibres is probably closely similar to that in the dog.

In the *cat*, the augmentor nerves spring from the ganglion stellatum, and very rarely from the inferior cervical ganglion as well. The right cardiac sympathetic nerve communicates with the vagus.

The stimulation of the sympathetic chain in the *frog*, "between ganglion 1 and the vagus ganglion, and also stimulation of the chain between ganglia 2

and 3, causes marked acceleration and augmentation of the auricular and ventricular contractions. Stimulation between ganglia 3 and 4 produces no effect whatever upon the heart." This experiment of Gaskell and Gadow's shows that augmentor fibres enter the sympathetic from the spinal cord along the ramus communicans of the third spinal nerve and pass upward in the sympathetic chain. In this animal the sympathetic chain, after dividing between the first and second ganglia to form the annulus of Vieussens, joins the trunk of the vagus between the united vagus and glosso-pharyngeal ganglia and the



FIG. 33.—The cardiac sympathetic nerves in *Rana temporaria* (twice natural size): V-Sy, vago-sympathetic; Ar, arteria vertebralis; II, IV, second and fourth spinal nerves (Gaskell and Gadow, 1894).

vertebral column (see Fig. 33). Here the sympathetic again divides, some of the fibres passing alongside the vagus into the cranial cavity, the rest accompanying the vagus nerve peripherally. The augmentor nerves for the heart are among the latter, for the stimulation of the intracranial vagus results in pure inhibition, while the stimulation of the vagus trunk after it is joined by the sympathetic may give either inhibition or augmentation. We may say, therefore, that the augmentor nerves of the frog pass out of the spinal cord by the

third spinal nerve, through the ramus communicans of this nerve, into the third sympathetic ganglion, up the sympathetic chain to the ganglion of the vagus, and down the vagus trunk to the heart.

**Stimulation of Augmentor Nerves.**—The most obvious effect of the stimulation of the augmentor nerves is an increase of from 7 to 70 per cent. in the frequency of the heart-beat (see Fig. 34). The quicker the heart is beating before the stimulation, the less marked is the acceleration. The absolute maxi-



FIG. 34.—Curve of blood-pressure in the cat, recorded by a mercury manometer, showing the increase in frequency of heart-beat from excitation of the augmentor nerves. The curve reads from right to left. The augmentor nerves were excited during thirty seconds, between the two stars. The number of beats per ten seconds rose from 24 to 33 (Boehm, 1875, p. 258).

mum of frequency is, however, independent of the frequency before stimulation. The maximum of acceleration is largely independent of the duration of stimulation. The duration of stimulation and the duration of acceleration are not related, a long stimulation causing no greater acceleration than a short one.

The force of the ventricular beat is increased. The ventricle is filled more completely by the auricles, the volume of the ventricle being increased. The

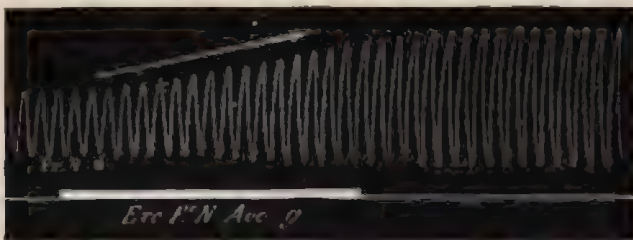


FIG. 35.—Increase in the force of the ventricular contraction (curve of pressure in right ventricle) from stimulation of augmentor fibres. There is little or no change in frequency (Frank, 1890, p. 819).

output of the heart is raised. There is no definite relation between the increase of contraction volume or force of contraction and the increase in frequency (see Fig. 35). Either may appear without the other, though this is rare. The simultaneous stimulation of the nerves of both sides does not give a greater maximum frequency than the stimulation of one nerve alone.

The strength and the volume of the auricular contractions are also increased. The increase in volume is not due to a rise of pressure in the veins—in fact, the pressure falls in the veins—but to a change in the elasticity of the relaxed auricle, a lowering of its tonus. This change is not related to the increase in the force of the auricular contractions that stimulation of the augmentor nerves also causes. It varies much in amount and is less constantly met with than the change in force. The changes in the ventricle and auricle



probably account for the rise of blood-pressure in the systemic arteries and the fall in both systemic and pulmonary veins observed by Roy and Adami.

The speed of the cardiac *excitation wave* is increased. Its passage across the auriculo-ventricular groove is also quickened, as is shown in the following experiment of Bayliss and Starling. In the dog, the artificial excitation of the ventricle may cause the excitation wave to travel in a reverse direction, namely, from ventricle to auricle. If the ventricles are excited rhythmically and the rate of excitation is gradually increased, a limit will be reached beyond which the auricle no longer beats in response to every ventricular contraction. With intact vagi, a rate of 3 per second is generally the limit. If now the augmentor nerve is stimulated, the "block" is partially removed, and the auricle beats during and for a short time after the stimulation at the same rapid rate as the ventricle.

The *latent period* of the excitation is long. In the dog, about two seconds pass between the beginning of stimulation and the beginning of acceleration, and ten seconds may pass before the maximum acceleration is reached. The after-effect may continue two minutes or more. It consists of a weakening of the contractions and an increase in the difficulty with which the excitation wave passes from the auricle to the ventricle. The return to the former frequency is more rapid after short than after long stimulations.

The effect upon the heart-rate of *simultaneous stimulation* of the vagi and accelerator nerves, according to Hunt, is determined by the relative strength of the two stimulating currents. For sub-maximal stimuli the result for both systole and diastole is approximately the arithmetical mean of the results of stimulating the two nerves separately.<sup>1</sup> The acceleration that is seen after the stimulation of the vagus is due to the after-effect of the stimulation of accelerating fibres in the vagus.

The simultaneous stimulation of the augmentors and the vagi, the strength of the current being sufficient to stop the auricular contractions, causes acceleration of the ventricular contractions.

The acceleration of the heart may be more or less intermittent, although the excitation of the augmentor nerves continues. It is probable that this is due to irradiation from the bulbar respiratory centre.<sup>2</sup>

#### OTHER CENTRIFUGAL HEART-NERVES.

In the vago-sympathetic trunk and the annulus of Vieussens fibres pass to the heart that cannot be classed either with the vagus or the augmentor nerves. The evidence for their existence is furnished by Roy and Adami's observation that when the intracardiac vagus mechanism is acting strongly, so that the auricles are more or less completely arrested, the stimulation of the vago-sympathetic trunk sometimes causes a decided increase in the force both of the ventricles and the auricles, usually accompanied by an acceleration of the rhythm of the heart. These changes are too rapidly produced to be augmentor effects.

<sup>1</sup> Hunt: *American Journal of Physiology*, 1899, ii. p. 422.

<sup>2</sup> Werthemier and Lepage: *Journal de physiologie et de pathologie générale*, 1899, p. 236.



Centrifugal inhibitory nerves have been found as an anomaly in the right depressor nerve of a rabbit.<sup>1</sup>

Pawlow divides the inhibitory and augmentor nerves into four classes—(1) nerves inhibiting the frequency of the beat, (2) nerves inhibiting the force of the contraction, (3) nerves augmenting frequency, and (4) nerves augmenting force. The origin of this subdivision of the two groups generally recognized was the observation that, in certain stages of convallaria poisoning, the excitation of the vagus in the neck—all the branches of the nerve except those going to heart and lungs being cut—reduced the blood-pressure without altering the frequency of the beat. Further researches showed that the stimulation of branch 3 (Fig. 36) even in unpoisoned animals reduced the blood-pressure independently of the variable alteration simultaneously produced in the pulse-rate. Stimulation of branch 5 produced an acceleration of the heart-beat without increase of blood-pressure. Other branches brought about rise of pressure without acceleration, and increased discharge by the left ventricle without alteration in the pulse-rate.

These results are supported further by Wooldridge's observation that excitation of the peripheral ends of certain nerves on the posterior surface of the ventricle raised the blood-pressure without modifying the frequency of contraction, and by Roy and Adami's demonstration that certain branches of the first thoracic ganglion lessen the force of the cardiac contraction without influencing its rhythm. But the matter is as yet far from certain.

#### THE CENTRIPETAL NERVES OF THE HEART.

**The Ventricular Nerves.**—When the mammalian heart is freed from blood by washing it out with normal saline solution and the ventricle is painted with pure carbolic acid, liquefied by warming, numerous nerves appear as white threads on a brown background. They are non-medullated, form many plexuses, and run beneath the pericardium obliquely downward from the base to the apex of the ventricle. They may be traced to the cardiac plexus. These fibres are not centrifugal branches of the vagus or the augmentor nerves, for the characteristic effects of vagus and augmentor stimulation are seen after section of the nerves in question. The stimulation of their peripheral ends, moreover, the fibre being carefully dissected out from the subpericardial tissue,

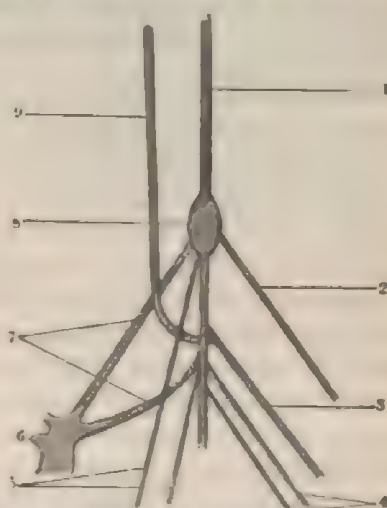


FIG. 36.—Schema of the centrifugal nerves of the heart according to Pawlow: 1, vagosympathetic nerve; 2, upper inner branch; 3, strong inner branch; 4, lower inner branch; 5, upper and lower outer branches; 6, ganglion stellatum; 7, annulus of Vieussens; 8, middle-inferior cervical ganglion; 9, recurrent laryngeal nerve.

<sup>1</sup> Hering: *Archiv für die gesamte Physiologie*, 1894, lvii. p. 78.

cut across, and the cut end raised on a thread in the air, is without effect on the blood-pressure and pulse-rate. The stimulation of the central stumps of these nerves, on the contrary, is followed by changes both in the blood-pressure and the pulse, showing that they carry impulses from the heart to the cardiac centres in the central nervous system, or perhaps, according to the views of some recent investigators, to peripheral ganglia, thus modifying the action of the heart reflexly.

**Sensory Nerves of the Heart.**—The stimulation of intracardiac nerves by the application of acids and other chemical agents to the surface of the heart causes various reflex actions, such as movements of the limbs. The afferent nerves in these reflexes are the vagi, for the reflex movements disappear when the vagi are cut. On the strength of these experiments the vagus has been believed to carry sensory impressions from the heart to the brain. Direct stimulation of the human heart, in cases in which a defect in the chest-wall has made the organ accessible, give evidence of a dim and very limited recognition of cardiac events—for example, the compression of the heart. Changes in the force, periodicity, and conduction of the contraction-wave may be produced by direct electrical stimulation of the ventricle. The centre of these reflexes probably lies in the bulb.<sup>1</sup>

**Vagus.**—The stimulation of the central end of the cut vagus nerve,<sup>2</sup> the other vagus being intact, causes a slowing of the pulse-rate. The section of the second vagus causes this retardation of the pulse to disappear, indicating that the stimulation of the central end of the one affects the heart reflexly through the agency of the other vagus. The blood-pressure is simultaneously affected, being sometimes lowered and sometimes raised, the difference seeming to depend largely on the varying composition of the vagus in different animals and in different individuals of the same species. The stimulation of the pulmonary branches, by gently forcing air into the lungs, loud speaking, singing, etc., is said to increase the frequency of the heart-beat. Yet the chemical stimulation of the mucous membrane of the lungs is alleged to slow the pulse-rate and lower the blood-pressure. Observers differ as to the results of stimulation of the central end of the laryngeal branches of the vagus on the pulse-rate and blood-pressure.

**Depressor Nerve.**—The earlier stimulations of the nerves that pass between the central nervous system and the heart, with the exception of the vagus, altered neither the blood-pressure nor the pulse-rate. Ludwig and Cyon suspected that the negative results were owing to the fact that the stimulations were confined to the end of the cut nerve in connection with the heart. Some of the nerves, they thought, should carry impulses from the heart to the brain, and such nerves could be found only by stimulation of the brain end of the cut nerve. They began their research for these afferent nerves with the branch which springs from the rabbit's vagus high in the neck and passes downward to the ganglion stellatum. Their suspicion was at once confirmed. The stimu-

<sup>1</sup> Muskenz: *Archiv für die gesammte Physiologie*, 1897, lxxi p 328.

<sup>2</sup> Hunt: *Journal of Physiology*, 1895, xvii, p 381.



lation of the central end of this nerve, called by Ludwig and Cyon the depressor, caused a considerable fall of the blood-pressure.

The depressor nerve arises in the rabbit by two roots, one of which comes from the trunk of the vagus itself, the other from a branch of the vagus, the superior laryngeal nerve. Frequently the origin is single; in that case it is usually from the *nervus laryngeus*.<sup>1</sup> The *nervus depressor* runs in company with the sympathetic nerve to the chest, where communications are made with the branches of the ganglion stellatum.

The stimulation of the peripheral end of the depressor nerve is without effect on the blood-pressure and heart-beat. The stimulation of the central end, on the contrary, causes a gradual fall of the general blood-pressure to the half or the third of its former height. After the stimulation is stopped, the blood-pressure returns gradually to its previous level.

Simultaneously with the fall in blood-pressure a lessening of the pulse-rate sets in. The slowing is most marked at the beginning of stimulation, and after rapidly reaching its maximum gives way gradually until the rate is almost what it was before the stimulation began. After stimulation the frequency is commonly greater than previous to stimulation.

After section of both vagi, the stimulation of the depressor causes no change in the pulse-rate, but the blood-pressure falls as usual. The alteration in frequency is therefore brought about through stimulation of the cardiac inhibitory centre, acting on the heart through the vagi. The experiment teaches, further, that the alteration in pressure is not dependent on the integrity of the vagi.

Poisoning with curare paralyzes all motor mechanisms except the heart and the muscles of the blood-vessels. Yet curare-poisoning does not affect the result of depressor stimulation. The cause of the fall in blood-pressure must be sought then either in the heart or the reflex dilatation of the blood-vessels. It cannot be in the heart, for depressor stimulation lowers the blood-pressure after all the nerves going to the heart have been severed. It must therefore lie in the blood-vessels. Ludwig and Cyon knew that the dilatation of the intestinal vessels could produce a great fall in the blood-pressure and turned at once to them. Section of the splanchnic nerve caused a dilatation of the abdominal vessels and a fall in the blood-pressure. Stimulation of the peripheral end of the cut splanchnic caused the blood-pressure to rise even beyond its former height. Ludwig and Cyon reasoned that if the depressor lowers the blood-pressure chiefly by affecting the splanchnic nerve reflexly, the stimulation of the central end of the depressor after section of the splanchnic nerves ought to have little effect on the blood-pressure. This proved to be the case. The investigators concluded that the depressor reduces the blood-pressure chiefly by lessening the tonus of the vessels governed by the splanchnic nerve, thus allowing their dilatation and in consequence lessening the peripheral resistance. The fallacy in this argument has recently been pointed out by Porter and Beyer.<sup>2</sup> The stimulation of the de-

<sup>1</sup> Tschirwinsky: *Centralblatt für Physiologie*, 1890, ix. p. 778, gives a somewhat different account.

<sup>2</sup> Porter and Beyer: *American Journal of Physiology*, 1900, xxiii.



pressor after section of the splanchnic nerves has little effect, because the blood-pressure is already so low when the stimulation is made that it can sink but little more. When, however, the pressure is restored to its normal level, after section of the splanchnic nerves by the stimulation of their peripheral ends, or by the injection of normal saline solution into the vessels and the depressors then stimulated, the fall in blood-pressure is nearly and sometimes quite as great as that obtained by the stimulation of the depressor nerve when the splanchnic nerves are intact. It is improbable, therefore, that the depressor acts chiefly through the splanchnic nerves. It probably acts on all the vasomotor nerves connected with the vasomotor centre. This view is somewhat strengthened by the observations of Bayliss (Fig. 37).

It has already been said that the depressor fibres pass from the heart to the vaso-motor mechanism in the central nervous system. The cardiac fibres are probably stimulated when the heart is overfilled through lack of expulsive force or through excessive venous inflow, and, by reducing the peripheral resistance, assist the engorged organ to empty itself.

The depressor nerve is not in continual action; it has no tonus; for the section of both depressor nerves causes no alteration in the blood-pressure.

Sewall and Steiner have obtained in some cases a permanent rise in blood-pressure following section of both depressors, yet they hesitate to say that the depressor exercises a tonic action.

Spallita and Consiglio have stimulated the depressor before and after the



FIG. 37.—Showing the fall in blood-pressure and the dilatation of peripheral vessels from stimulation of the central end of the depressor nerve (Bayliss: A, curve of blood-pressure in the carotid artery; B, volume of hind limb, recorded by a plethysmograph; C, electro-magnet line, in which the elevation shows the time of stimulation of the nerve; D, atmospheric pressure-line. E, time in seconds.

section of the spinal accessory nerve near its junction with the vagus. They find that after section of the spinal accessory, the stimulation of the depressor does not affect the pulse, whence they conclude that the depressor fibres that affect the blood-pressure are separate from those that affect the rate of beat, the latter being derived from the spinal accessory nerve.

A recent study by Bayliss<sup>1</sup> brings out several new facts. If a limb is placed

<sup>1</sup> Bayliss: *Journal of Physiology*, 1893, xiv p. 303. The relation between the depressor nerve and the thyroid is pointed out by v. Cyon: *Centralblatt für Physiologie*, 1897, ii pp. 279, 357.

in Moeso's plethysmograph and the central end of the depressor stimulated, the volume of the limb increases, showing an active dilatation of the vessels that supply it. The latent period of this dilatation varies greatly. The vessels of the skin play a large part in its production. A similar local action is seen on the vessels of the head and neck (see Fig. 37).

The depressor fibres vary much in size in different animals. When the nerve is small, a greater depressor effect can be obtained by stimulating the central end of the vagus than from the depressor itself. But the course of the fall is different in the two cases. With the depressor, the fall is maintained at a constant level during the whole excitation, however long it lasts, whereas in the case of the vagus the pressure very soon returns to its original height although the excitation still continues. Bayliss believes, therefore, that there is a considerable difference between the central connections of the depressor nerve itself and the depressor fibres sometimes found in other nerves.

The left depressor nerve usually produces a greater fall of pressure than the right. The excitation of the second nerve during the excitation of the first produces a greater fall than the excitation of one alone.

The fibres of the depressor, in part at least, end in the wall of the ventricle. A similar nerve has been demonstrated in the cat, horse, dog, sheep, swine, and in man.

**Sensory Nerves.**—The first and usually the only effect of the stimulation of the central end of a mixed nerve like the sciatic, according to Roy and Adami, is an increase in the force and the frequency of the heart-beat. Other observers have sometimes found quickening and sometimes slowing of the pulse-rate, so that sensory nerves, as Tigerstedt suggests, appear to affect both the inhibitory and the augmenting heart-nerves. When a sensory nerve is weakly excited the augmentor effect predominates, when strongly excited the inhibitory. A well-known demonstration of the reflex action of the sensory nerves on the heart is seen in the slowing of the rabbit's heart when the animal is made to inhale chloroform. The superior laryngeal and the trigeminal nerves, especially the latter, convey the stimulus to the nerve-centres.

The stimulation of the *nerves of special sense*, optic, auditory, olfactory and glosso-pharyngeal nerves, also sometimes slows and sometimes quickens the heart.

**Sympathetic.**—The reflex action of the sympathetic nerve upon the heart is well shown by the celebrated experiment of F. Goltz. In a medium-sized frog, the pericardium was exposed by carefully cutting a small window in the chest-wall. The pulsations of the heart could be seen through the thin pericardial membrane. Goltz now began to beat upon the abdomen about 140 times a minute with the handle of a scalpel. The heart gradually slowed, and at length stood still in diastole. Goltz now ceased the rain of little blows. The heart remained quiet for a time and then began to beat again, at first slowly and then more rapidly. Some time after the experiment, the heart beat about five strokes in the minute faster than before the experiment was begun. The effect cannot be obtained after section of the vagi.



Bernstein found that the afferent nerves in Goltz's experiment were branches of the abdominal sympathetic, and discovered that the stimulation of the central end of the abdominal sympathetic in the rabbit was followed also by reflex inhibition of the heart.

The stimulation of the central end of the splanchnic produces a reflex rise of blood-pressure and, perhaps secondarily, a slowing of the heart. In some cases acceleration has been observed. According to Roy and Adami splanchnic stimulation sometimes produces a combination of augmentor and vagus effects, the augmentation appearing during stimulation and giving place abruptly to well-marked inhibitory slowing at the close of stimulation.

The results of stimulating various abdominal viscera have been studied by Mayer and Pribram. One of the most interesting of the reflexes observed by them was the inhibition of the heart called forth by dilating the stomach.

The stimulation of the cervical sympathetic does not give any very constant results on the action of the heart.

#### B. THE CENTRES OF THE HEART-NERVES.

**Inhibitory Centre.**—It has been already mentioned that the brothers Weber localized the cardiac inhibitory centre in the medulla oblongata. The efforts to fix the exact location of the centre by stimulation of various parts, either mechanically, by thrusting fine needles into the medulla, or electrically, cannot inspire great confidence because of the difficulty of distinguishing between the results that follow the excitation of a nerve-path from or to the centre and those following the excitation of the centre itself. According to Laborde, who also used this method, the cardiac inhibitory centre is situated at the level of the mass of cells known as the accessory nucleus of the hypoglossus and the mixed nerves (vagus, spinal accessory, glosso-pharyngeal).

The localization of the centre by the method of successive sections is perhaps more trustworthy. Franek has found that the separation of the bulb from the spinal cord cuts off the reflexes called forth by nerves that enter the spinal cord, while leaving undisturbed the reflex produced by stimulation of the trigeminal nerve.

On the whole, there seems to be no doubt that the cardiac inhibitory centre is situated in the bulb.

**Tonus of Cardiac Inhibitory Centre.**—The cardiac inhibitory centre is probably always in action, for when the vagus nerves are cut, the heart-beat becomes more frequent.<sup>1</sup> The source of this continued or "tonic" activity may lie in the continuous discharge of inhibitory impulses created by the liberation of energy in the cell independent of direct external influences, or the cells may be discharged by the continuous stream of afferent impulses that must constantly play upon them from the multitude of afferent nerves. This latter theory, the conception of a reflex tonus, is made probable by the observations that section of the vagi does not increase the rate of beat after the greater part of the afferent impulses have been cut off by division of the

<sup>1</sup> Hunt: *American Journal of Physiology*, 1899, ii p. 397.



spinal cord near its junction with the bulb, and that the sudden-decrease in the number of afferent impulses caused by section of the splanchnic nerve quickens the pulse-rate.

*Irradiation.*—The slowing of the rate of beat observed chiefly during the expiratory portion of respiration disappears after the section of both vagus nerves. The slowing may perhaps be due to the stimulation of the cardiac inhibitory centre by irradiation from the respiratory centre.<sup>1</sup>

*Origin of Cardiac Inhibitory Fibres.*—Since the researches of Waller and others, it has been generally believed that the cardiac inhibitory fibres enter the vagus from the spinal accessory nerve, for the reason that cardiac inhibition was not secured in animals in which the fibres in the vagus derived from the spinal accessory nerve were made to degenerate by tearing out the latter before its junction with the vagus. These results have lately been called in question by Grossmann.<sup>2</sup> The method employed by his predecessors, according to him, probably involved the destruction of vagus roots as well as those of the spinal accessory. Grossmann finds that the stimulation of the spinal accessory nerve before its junction with the vagus does not inhibit the heart. Nor does inhibition follow the stimulation of the bulbar roots supposed to be contributed to the mixed nerve by the spinal accessory.

*Augmentor Centre.*—The situation of the centre for the augmentor nerves of the heart is not definitely known, although from analogy it seems probable that it will be found in the bulb. That this centre is constantly in action is indicated by the lowering of the pulse-rate after section of the vagi followed by the bilateral extirpation of the inferior cervical and first thoracic ganglia.<sup>3</sup> The division of the spinal cord in the upper cervical region after the section of the vagi has the same effect. Vagus inhibition, moreover, is said to be more readily produced after section of the augmentor nerves.

McWilliam<sup>4</sup> has remarked that the latent period and the character of the acceleration often accompanying the excitation of afferent nerves may differ entirely from the characteristic effects of the excitation of augmentor nerves. The stimulation of the latter is followed by a long latent period, after which the rate of beat gradually increases to its maximum and, after excitation is over, as gradually declines. The excitation of an afferent nerve, on the contrary, causes often, with almost no latent period, a remarkably sudden acceleration, that reaches at once a high value and often suddenly gives way to a slow heart-beat. These facts seem to show that reflex acceleration of the heart-beat is due to changes in the cardiac inhibitory centre, and not to augmentor excitation. This view is strengthened by the fact that if the augmentor nerves are cut, the vagi remaining intact, the stimulation of afferent fibres, for example in the brachial nerves, can still cause a marked quickening of the pulse-rate. In short, the action of afferent nerves upon the rate of beat is essentially

<sup>1</sup> Launanié: *Comptes rendus Société de Biologie*, 1893, p. 723. Compare Wood: *American Journal of Physiology*, 1899, ii. p. 352.

<sup>2</sup> Grossmann: *Archiv für die gesammte Physiologie*, 1895, lix. p. 6.

<sup>3</sup> Hunt: *American Journal of Physiology*, 1899, ii. p. 397.

<sup>4</sup> McWilliam: *Proceedings Royal Society*, 1893, lili. p. 472.

the same, according to this observer, whether the augmentor nerves are divided or intact.

Roy and Adami believe that the stimulation of afferent nerves, such as the sciatic or the splanchnic, excites both augmentor and vagus centres. The augmentor centre is almost always the more strongly excited of the two, so that augmentor effects alone are usually obtained.

**Action of Higher Parts of the Brain on Cardiac Centres.**—Repeated efforts have been made to find areas in the cortex of the brain especially related to the inhibition or augmentation of the heart, but with results so contradictory as to warrant the conclusion that the influence on the heart-beat of the parts of the brain lying above the cardiac centres does not differ essentially from that of other organs peripheral to those centres.

Voluntary control of the heart, by which is meant the power to alter the rate of beat by the exercise of the will, is impossible except as a rare individual peculiarity, commonly accompanied by an unusual control over muscles, such as the platysma, not usually subject to the will. Cases are described by Tarchanoff and Pease, in which acceleration of the beat up to twenty-seven in the minute was produced, together with increase of blood-pressure, from vaso-constrictor action. The experiments are dangerous.<sup>1</sup>

**Peripheral Reflex Centres.**—It is now much discussed whether the peripheral ganglia can act as centres of reflex action. According to Franck<sup>2</sup> the excitation of the central stump of the divided left anterior limb of the annulus of Vieussens is transformed within the first thoracic ganglion, isolated from the spinal cord by section of its rami communicantes, into a motor impulse transmitted by the posterior limb of the annulus. This motor impulse causes, independently of the bulbo-spinal centres, a reflex augmentation in the action of the heart, and a reflex constriction of the vessels in the external ear, the submaxillary gland, and the nasal mucous membrane. This experiment, in conjunction with the facts in favor of other sympathetic ganglia acting as reflex centres,<sup>3</sup> seems to demonstrate that some afferent impulses are transformed in the sympathetic cardiac ganglia into efferent impulses modifying the action of the heart. If this conclusion is confirmed by future investigations it will profoundly modify the views now entertained regarding the innervation of the heart.

The experiments of Stannius, published in 1852, have been the starting-point of a very great number of researches on the innervation of the frog's heart. Stannius observed, among other facts, that the heart remained for a time arrested in diastole when a ligature was tied about the heart precisely at the junction of the sinus venosus with the right auricle. No sufficient explanation of this result has yet been given, nor is one likely to be found until the innervation of the heart is better understood. Stannius further

<sup>1</sup> Van de Velde: *Archiv für die gesammte Physiologie*, 1897, lxxvi p. 232.

<sup>2</sup> Franck: *Archiv de Physiologie*, 1894, p. 721.

<sup>3</sup> Langley and Anderson: *Journal of Physiology*, 1894, xvi, p. 435. The attempt of Prof. Kronecker to demonstrate a co-ordinating centre in the ventricles may be mentioned here (*Zeitschrift für Biologie*, 1896, xxxiv, p. 529).



observed that after the ligature just described had been drawn tight, thus arresting the heart, the placing of a second ligature around the heart at the junction of the auricle and ventricle caused the latter to begin to beat again, while the auricle remained at rest. This second ligature, it is generally admitted, stimulates the ganglion of Bidder, and the ventricle responds by rhythmic contractions to the constant excitation thus produced. Loosening the ligature and so interrupting the excitation stops the ventricular beat.

### PART III.—THE NUTRITION OF THE HEART.

The cells of which the heart-wall are composed are nourished by contact with a nutrient fluid. In hearts consisting of relatively few cells no special means of bringing the nutrient fluid to the cells is required. The walls of the minute globular heart of the small crustacean *Daphnia*, for example, are composed of a single layer of cells, each of which is bathed by the fluid which the heart pumps. In larger hearts with thicker walls only the innermost cells could be fed in this way. Special means of distributing the blood throughout the substance of the organ are necessary here.

**Passages in the Frog's Heart.**—In the frog this distribution is accomplished chiefly through the irregular passages which go out from the cavities of the heart between the muscle-bundles to within even the fraction of a millimeter of the external surface. These passages vary greatly in size. Many are mere capillaries. They are lined by a prolongation of the endothelium of the heart. Filled by every diastole and emptied by every systole, they do the work of blood-vessels and carry the blood to every part of the cardiac muscle.

Henri Martin<sup>1</sup> describes a coronary artery in the frog, analogous to the coronary arteries of higher vertebrates. This artery supplies a part of the auricles and the upper fourth of the ventricle.

In the rabbit, cat and dog, and in man a well-developed system of cardiac vessels exists, the coronary arteries and veins. Their distribution in the dog deserves especial notice, because the physiological problems connected with these vessels have been studied chiefly in this animal.

**Coronary Arteries in the Dog.**—In the dog the coronary arteries and their larger branches lie upon the surface of the heart, covered as a rule only by the pericardium and a varying quantity of connective tissue and fat. The left coronary artery is extraordinarily short. A few millimeters after its origin from the aorta it divides into the large ramus circumflex and the descendens, nearly as large. The former runs in the auriculo-ventricular furrow around the left side of the heart to the posterior surface, ending in the posterior inter-ventricular furrow. The left auricle and the upper anterior and the posterior portion of the left ventricle are supplied by this artery. The descendens runs downward in the anterior inter-ventricular furrow to the apex. Close to its origin the descendens gives off the arteria septi, which at once enters the

<sup>1</sup> Martin : *Comptes rendus Société de Biologie*, 1893, p. 754.



inter-ventricular septum and passes, sparsely covered with muscle-bundles, obliquely downward and backward on the right side of the septum. The descendens in its farther course gives off numerous branches to the left ventricle and the anterior part of the septum. Only a few small branches go to the right ventricle. Thus the descendens supplies the septum and the inferior anterior part of the left ventricle. The right coronary artery, imbedded in fat, runs in the right auriculo-ventricular groove around the right side of the heart, supplying the right auricle and ventricle. It is a much smaller artery than either the circumflex or descendens. Each coronary artery keeps to its own boundaries and does not, in the dog, pass into the field of another artery, as sometimes happens in man.<sup>1</sup>

**Terminal Nature of Coronary Arteries.**—The coronary arteries in the dog, as in man, are terminal arteries, that is, the anastomoses which their branches have with neighboring vessels do not permit the making of a collateral circulation. Their terminal nature in the human heart is shown by the formation of infarcts in the areas supplied by arteries which have been plugged by embolism or thrombosis. That part of the heart-wall supplied by the stopped artery speedily decays. The bloodless area is of a dull white color, often faintly tinged with yellow; rarely it is red, being stained by hæmoglobin from the neighboring capillaries. The cross section is coarsely granular. The nuclei of the muscle-cells have lost their power of staining. The muscle-cells are dead and connective tissue soon replaces them.<sup>2</sup> This loss of function and rapid decay of cardiac tissue would not take place did anastomoses permit the establishment of collateral circulation between the artery going to the part and neighboring arteries. The terminal nature of the coronary arteries in the dog has been placed beyond doubt by direct experiment. It is possible to tie them and keep the animal alive until a distinct infarct has formed.<sup>3</sup>

The objection that one of the coronary arteries can be injected from another,<sup>4</sup> and that therefore they are not terminal, is based on the incorrect premise that terminal arteries cannot be thus injected, and has no weight against the positive evidence of the complete failure of nutrition following closure. The passage of a fine injection-mass from one vascular area to another proves nothing concerning the possibility of the one area receiving its blood-supply from the other. Such supply is impossible if the resistance in the communicating vessels is greater than the blood-pressure in the smallest branches of the artery through which the supply must come. It is the fact of this high resistance, due to the small size of the communicating branches, which makes the artery "terminal." This condition of high resistance is really present during life, or infarction could not take place.

The terminal nature of the coronary arteries is of great importance with regard to the part taken by them in the nutrition of the heart. Being ter-

<sup>1</sup> Baumgarten: *American Journal of Physiology*, 1899, ii. p. 243.

<sup>2</sup> See also the description by Kolster: *Skandinavisches Archiv für Physiologie*, 1893, iv. p. 14, of the infarctions produced experimentally in the dog's heart.

<sup>3</sup> Porter: *Archiv für die gesammte Physiologie*, 1893, iv. p. 366.

<sup>4</sup> Michaelis: *Zeitschrift für klinische Medizin*, 1894, xxiv. p. 289.

minimal, their experimental closure enables us to study the effects of the sudden stopping of the blood-supply (ischæmia) of the heart muscle upon the action of the heart.

**Results of Closure of the Coronary Arteries.**—The sudden closure of one of the large coronary branches in the dog has as a rule either no effect upon the action of the heart beyond occasional and transient irregularity,<sup>1</sup> or is followed after the lapse of seconds, or of minutes, by the arrest of the ventricular stroke, the ventricle falling a moment later into the rapid, fluttering,

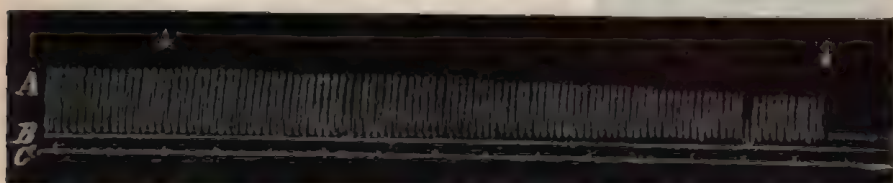


FIG. 38.—A, curve of intra-ventricular pressure, written by a manometer connected with the interior of the left ventricle; B, atmospheric pressure; C, time in two-second intervals. At the first arrow the ramus circumflexus of the left coronary artery was ligated; at the second arrow the heart fell into fibrillary contractions. The lessening height of the curve shows the gradual diminution of the force of contraction after ligation. The rise of the lower line of the curve above the atmospheric pressure indicates a rise of intra-ventricular pressure during diastole. The small elevations in the pressure curve after the second arrow are caused by the left auricle, which continued to beat after the arrest of the ventricle (Porter, 1893).

undulatory movements known as fibrillary contractions and produced by the inco-ordinated, confused shortenings of individual muscle-cells, or groups of cells. The auricles continue to beat for a time, but the power of the ventricles to execute co-ordinated contractions is lost.

**The Frequency of Arrest.**—The frequency with which closure is followed by ventricular arrest depends on at least two factors—namely, the size of the artery ligated and the irritability of the heart. That the size of the artery is of influence appears from a series of ligations performed on dogs, arrest being never observed after ligation of the arteria septi alone, rarely observed (14 per cent.) with the right coronary artery, more frequently (28 per cent.) with the descendens, and still more frequently (80 per cent.) with the arteria circumflexa.<sup>2</sup> The irritability of the heart is an important factor. In animals cooled by long artificial respiration, or by section of the spinal cord at its junction with the bulb, the ligation of the descendens arrests the heart less frequently than in vigorous animals which have been operated upon quickly. The frequency of arrest is increased by the use of morphia and curare.<sup>3</sup>

**Changes in the Heart-beat.**—Ligation destined to arrest the heart is followed almost immediately by a continuous fall in the intra-ventricular pressure during systole and a gradual rise in the pressure during diastole (see Fig. 38). The contraction and relaxation of the ventricle are often slowed. The force of the ventricular stroke is diminished. As arrest draws near, irregularities in the force of the ventricular beat are seldom absent. The frequency of beat is sometimes unchanged throughout, but is usually diminished toward the end;

<sup>1</sup> The changes produced by subsequent degeneration are not considered here.

<sup>2</sup> Porter: *Journal of Physiology*, 1893, xv. p. 131.

<sup>3</sup> Porter: *Journal of Experimental Medicine*, 1896, i. p. 49.



cut across, and the cut end raised on a thread in the air, is without effect on the blood-pressure and pulse-rate. The stimulation of the central stumps of these nerves, on the contrary, is followed by changes both in the blood-pressure and the pulse, showing that they carry impulses from the heart to the cardiac centres in the central nervous system, or perhaps, according to the views of some recent investigators, to peripheral ganglia, thus modifying the action of the heart reflexly.

**Sensory Nerves of the Heart.**—The stimulation of intracardiac nerves by the application of acids and other chemical agents to the surface of the heart causes various reflex actions, such as movements of the limbs. The afferent nerves in these reflexes are the vagi, for the reflex movements disappear when the vagi are cut. On the strength of these experiments the vagus has been believed to carry sensory impressions from the heart to the brain. Direct stimulation of the human heart, in cases in which a defect in the chest-wall has made the organ accessible, give evidence of a dim and very limited recognition of cardiac events—for example, the compression of the heart. Changes in the force, periodicity, and conduction of the contraction-wave may be produced by direct electrical stimulation of the ventricle. The centre of these reflexes probably lies in the bulb.<sup>1</sup>

**Vagus.**—The stimulation of the central end of the cut vagus nerve,<sup>2</sup> the other vagus being intact, causes a slowing of the pulse-rate. The section of the second vagus causes this retardation of the pulse to disappear, indicating that the stimulation of the central end of the one affects the heart reflexly through the agency of the other vagus. The blood-pressure is simultaneously affected, being sometimes lowered and sometimes raised, the difference seeming to depend largely on the varying composition of the vagus in different animals and in different individuals of the same species. The stimulation of the pulmonary branches, by gently forcing air into the lungs, loud speaking, singing, etc., is said to increase the frequency of the heart-beat. Yet the chemical stimulation of the mucous membrane of the lungs is alleged to slow the pulse-rate and lower the blood-pressure. Observers differ as to the results of stimulation of the central end of the laryngeal branches of the vagus on the pulse-rate and blood-pressure.

**Depressor Nerve.**—The earlier stimulations of the nerves that pass between the central nervous system and the heart, with the exception of the vagus, altered neither the blood-pressure nor the pulse-rate. Ludwig and Cyon suspected that the negative results were owing to the fact that the stimulations were confined to the end of the cut nerve in connection with the heart. Some of the nerves, they thought, should carry impulses from the heart to the brain, and such nerves could be found only by stimulation of the brain end of the cut nerve. They began their research for these afferent nerves with the branch which springs from the rabbit's vagus high in the neck and passes downward to the ganglion stellatum. Their suspicion was at once confirmed. The stimu-

<sup>1</sup> Munkens: *Archiv für die gesammte Physiologie*, 1897, lxvi p 328.

<sup>2</sup> Hunt: *Journal of Physiology*, 1895, xviii. p 391.



lation of the central end of this nerve, called by Ludwig and Cyon the depressor, caused a considerable fall of the blood-pressure.

The depressor nerve arises in the rabbit by two roots, one of which comes from the trunk of the vagus itself, the other from a branch of the vagus, the superior laryngeal nerve. Frequently the origin is single; in that case it is usually from the nervus laryngeus.<sup>1</sup> The nervus depressor runs in company with the sympathetic nerve to the chest, where communications are made with the branches of the ganglion stellatum.

The stimulation of the peripheral end of the depressor nerve is without effect on the blood-pressure and heart-beat. The stimulation of the central end, on the contrary, causes a gradual fall of the general blood-pressure to the half or the third of its former height. After the stimulation is stopped, the blood-pressure returns gradually to its previous level.

Simultaneously with the fall in blood-pressure a lessening of the pulse-rate sets in. The slowing is most marked at the beginning of stimulation, and after rapidly reaching its maximum gives way gradually until the rate is almost what it was before the stimulation began. After stimulation the frequency is commonly greater than previous to stimulation.

After section of both vagi, the stimulation of the depressor causes no change in the pulse-rate, but the blood-pressure falls as usual. The alteration in frequency is therefore brought about through stimulation of the cardiac inhibitory centre, acting on the heart through the vagi. The experiment teaches, further, that the alteration in pressure is not dependent on the integrity of the vagi.

Poisoning with curare paralyzes all motor mechanisms except the heart and the muscles of the blood-vessels. Yet curare-poisoning does not affect the result of depressor stimulation. The cause of the fall in blood-pressure must be sought then either in the heart or the reflex dilatation of the blood-vessels. It cannot be in the heart, for depressor stimulation lowers the blood-pressure after all the nerves going to the heart have been severed. It must therefore lie in the blood-vessels. Ludwig and Cyon knew that the dilatation of the intestinal vessels could produce a great fall in the blood-pressure and turned at once to them. Section of the splanchnic nerve caused a dilatation of the abdominal vessels and a fall in the blood-pressure. Stimulation of the peripheral end of the cut splanchnic caused the blood-pressure to rise even beyond its former height. Ludwig and Cyon reasoned that if the depressor lowers the blood-pressure chiefly by affecting the splanchnic nerve reflexly, the stimulation of the central end of the depressor after section of the splanchnic nerves ought to have little effect on the blood-pressure. This proved to be the case. The investigators concluded that the depressor reduces the blood-pressure chiefly by lessening the tonus of the vessels governed by the splanchnic nerve, thus allowing their dilatation and in consequence lessening the peripheral resistance. The fallacy in this argument has recently been pointed out by Porter and Beyer.<sup>2</sup> The stimulation of the de-

<sup>1</sup> Tschirwinsky: *Centralblatt für Physiologie*, 1896, ix, p. 778, gives a somewhat different account.

<sup>2</sup> Porter and Beyer: *American Journal of Physiology*, 1900, xxiii.

brinated blood through the coronary vessels.<sup>1</sup> Recovery has also been obtained by passing immediately (within 15 seconds) a very rapid alternating current of not too great intensity.<sup>2</sup>

**Closure of the Coronary Veins.**—Closure of all the coronary veins in the rabbit produced fibrillary contractions after from fifteen to twenty minutes had passed. Their closure in the dog is said to be without effect<sup>3</sup>—a negative result perhaps to be explained by the fact that a portion of the coronary blood finds its way to the cavities of the heart through the venæ Thebesii.

**Volume of Coronary Circulation.**—Bohr and Henriques,<sup>4</sup> taking the average of six experiments on dogs, found that 16 cubic centimeters of blood passed through the coronary arteries per minute for each 100 grams of heart muscle. The quantity passing through both coronary arteries varied in different animals from 20 to 64 cubic centimeters per minute; the quantity passing through the left coronary artery varied from 22.5 to 60 cubic centi-



FIG. 40.—Diminution of the force of contraction of the ventricle of the isolated cat's heart in consequence of diminishing the supply of blood to the cardiac muscle. *A*, blood-pressure at the root of the aorta, recorded by a mercury manometer; *B*, intra-ventricular pressure-curve, left ventricle; the individual beats do not appear, because of the slow speed of the smoked surface; *C*, time in seconds; *D*, the number of drops of blood passing through the coronary arteries, each vertical mark recording one drop. As the number of drops of blood passing through the coronary arteries diminishes, the contractions of the left ventricle become weaker, but recover again when the former volume of the coronary circulation is restored.

eters per minute. The hearts weighed from 51 to 350 grams. The method which Bohr and Henriques found it necessary to employ placed the heart under such abnormal conditions that their results can be regarded as only approximate. Porter<sup>5</sup> supplied the left coronary artery of the dog with blood diluted one-half with sodium chloride solution (0.6 per cent.) by means of a tube (lumen 2.75 millimeters) inserted into the aortic opening of the left coro-

<sup>1</sup> Porter: *American Journal of Physiology*, 1898, i. p. 71.

<sup>2</sup> Prevost and Battelli: *Journal de physiologie et de pathologie générale*, 1900, p. 440.

<sup>3</sup> Michaelis: *Zeitschrift für klinische Medizin*, 1894, xxiv. p. 291.

<sup>4</sup> Bohr and Henriques: *Skandinavisk Archiv für Physiologie*, 1895, v. p. 232.

<sup>5</sup> Porter: *Journal of Experimental Medicine*, 1896, i. p. 64.



nary artery and connected with a reservoir placed 150 centimeters above the heart. In one dog, weighing 11,500 grams, 318 cubic centimeters flowed through in eight minutes. In a second dog, weighing 9500 grams, 114 cubic centimeters passed through in four minutes. In the isolated heart of the cat strong and regular contractions are made on a circulation of about 4 cubic centimeters per minute, or even less, through the coronary system. The quantity passing through the veins of Thebesius into the left auricle and ventricle is very slight.

The supply of blood to the heart-muscle is modified by ventricular contraction, not only in that the mean blood-pressure in the aorta is a function of the force of the heart-beat, but directly by the compression of the intramural vessels during systole. Thus, when a piece of the mammalian ventricle is kept beating by supplying it with defibrinated blood through its nutrient artery at a constant pressure, each beat can be seen to force the blood out of the severed vessels in the margin of the fragment. The effect of the contractions on the contents of the intramural vessels can also be demonstrated in the living animal by incising a vein, or a ligated artery on the distal side of the ligature, and slowing the heart by stimulation of the vagus. At each systole of the ventricle blood is forced from the vessel. Moreover, lessening the frequency of contraction diminishes the volume of the coronary circulation—*i. e.*, the outflow from the coronary veins, as may be shown in a record similar to that illustrated by Fig. 40. It is conceivable that the emptying of the intramural vessels by the contraction of the heart may favor the flow of blood through the heart-walls in two ways: first, by the diminished resistance which the empty patulous vessels should offer to the inflow of blood from the aorta when the heart relaxes; and, secondly, by the suction which might accompany the sudden expansion of the compressed vessels—expanding either by virtue of their intrinsic elasticity, or because of the pull of the surrounding tissues upon their walls, as the heart quickly regains its diastolic form. The problem thus raised may be attacked by suddenly connecting the distal portion of a coronary artery in the strongly beating heart of the living animal with a small reservoir of normally warm defibrinated blood at the atmospheric pressure. The connection can be made through a cannula tied into the artery (*ramus descendens* of the dog) or through a tube passed into the left coronary artery by way of the innominate artery and aorta. If each compression of the deeper branches of the artery were followed by an expansion sufficient to cause a noteworthy suction, the blood in the reservoir should be drawn into the artery, for this blood is the sole source of supply throughout the experiment, as the "terminal" nature of the coronary arteries prevents any material backflow from the distal branches. The results of these experiments showed that no appreciable suction can be demonstrated in the larger coronary arteries, even when a very sensitive minimum valve is interposed between the artery and the reservoir in order to prevent the possible masking of the suction by rising pressure accompanying the contraction of the ventricle. It is, therefore, necessary



to conclude that the emptying of the intramural vessels by the contraction of the heart favors the flow of blood through the heart-walls chiefly by the diminished resistance which the empty patulous vessels offer to the inflow from the aorta when the heart relaxes.<sup>1</sup>

**The Vessels of Thebesius and the Coronary Veins.**—The vessels of Thebesius probably have a part in the nutrition of the heart. If a glass tube two or three inches long is tied into the ventricle of the extirpated heart of the cat and filled with warm defibrinated blood, the heart will begin to beat, and, if the blood is oxygenated from time to time, may continue its contractions for many hours, although its only supply is through the vessels of Thebesius. If a vein on the surface of the ventricle is incised, the blood which enters the ventricle arterial in color will emerge from the cut vein a dark venous hue, showing that it has given up its oxygen and presumably other nutrient substances on its way through the heart-wall. This experiment also demonstrates a connection between the coronary vessels and the vessels of Thebesius; the same may be shown by corrosion preparations of hearts, the veins of which have been injected with celloidin.

The extirpated heart may be kept contracting a longer time, when to the supply received through the vessels of Thebesius is added that which may reach the heart from the auricle by backflow through the coronary veins, the valves of which are incompetent.

It is evident that these accessory channels of nutrition must be of importance when the main supply through the arteries is diminished, as in arteriosclerosis.<sup>2</sup>

**Blood-supply and Heart-beat.**—The relation between the volume of blood passing through the coronary arteries and the rate and force of the ventricular contraction has been studied by Magrath and Kennedy.<sup>3</sup> Variations in the volume of the coronary circulation in the isolated heart of the cat, unless very considerable, are not accompanied by changes in the rate of beat. The force of contraction, on the contrary, appears to be closely dependent on the volume of the coronary circulation (Fig. 40).

Distention of the ventricle diminishes the volume of blood flowing through the coronary vessels, except when this effect is compensated by the distention stimulating the ventricle to contract more forcibly, and thus to pump more blood through its walls by alternate compression and expansion of the intramural vessels.<sup>4</sup>

**Lymphatics of the Heart.**—A rich plexus of lymphatic vessels has been demonstrated in the heart.<sup>5</sup> Valuable information concerning the nutrition of the heart could probably be gained by the systematic study of these vessels.

<sup>1</sup> Porter: *American Journal of Physiology*, 1898, i. p. 145; consult also von Vintschgau: *Archiv für die gesamte Physiologie*, 1896, lxiv. p. 79.

<sup>2</sup> Pratt: *Ibid.*, p. 86.

<sup>3</sup> Magrath and Kennedy: *Journal of Experimental Medicine*, 1897, ii. p. 13.

<sup>4</sup> I. H. Hyde: *American Journal of Physiology*, 1898, i. p. 215.

<sup>5</sup> Nyström: *Archiv für Physiologie*, 1897, p. 361.

## C. SOLUTIONS WHICH MAINTAIN THE BEAT OF THE HEART.

The beat of the heart is maintained during life by a constant supply of oxygenated blood. The blood, however, is a very complex fluid, and it can hardly be supposed that all of its constituents are of equal value to the heart. The systematic search for those constituents of the blood which are of importance to the nutrition of the heart was begun in Ludwig's laboratory in 1875 by Merunowicz. The first step toward the method used by Merunowicz and his successors was taken by Cyon. Cyon tied cannulas in the vena cava inferior and in one of the aortæ of the extirpated heart of the frog, and joined them by a bowed tube filled with serum. The ventricle pumped the serum through the aortic cannula and the bowed tube into the vena cava, whence it reached the ventricle again. The force of the contraction was measured by a mercury manometer which was joined by a side branch to one limb of the bowed tube.

The frog heart manometer method thus introduced by Ludwig and Cyon has undergone various modifications at the hands of Blasius and Fick, Bowditch, Luciani, Kronecker, and others. Blasius and Fick were the first to register changes in the volume of the heart by the plethysmographic method, the organ being enclosed in a vessel filled with normal saline solution and connected with a manometer. This idea reappears in the Strassburg apparatus described below.

A valuable improvement was made by Kronecker, who invented a double cannula, through one side of which the "nutrient" fluid enters the ventricle while it passes out through the other (Fig. 41). The contents of the ventricle are thus continually renewed. In 1878, Roy constructed the instrument shown in Figure 42, by means of which the changes in the volume of the heart at each contraction are recorded on a moving cylinder. A great advance was made by Williams, in the invention known as "Williams's valve," which is the essential feature of the apparatus devised by this investigator and others in Schmiedeberg's laboratory at Strassburg. The present form of this apparatus is illustrated in Figure 43. A perfusion cannula is introduced into the ventricle through the aorta. Through one tube of the cannula the heart is fed from a reservoir placed above it. Through the other the heart pumps its contents into a higher reservoir or into the same reservoir. Thus the heart is "loaded" with a column of liquid of known height and pumps against a measurable resistance. A Williams valve in the inflow tube prevents any flow except in the direction of the heart. A similar valve reversed in the outflow tube prevents any flow



FIG. 41.—The perfusion cannula of Kronecker. The ventricle is tied on the cannula at *d*, a ring being placed here to prevent the ligature from slipping. The double tube, shown in cross section at *c*, divides into the large branch *a* and the small branch *b*. The nutrient solution enters the heart through *b* and escapes through *a*. The silver wire *c* can be connected with one pole of a battery, the cannula serving as one electrode, and the fluid surrounding the heart as the other.



except away from the heart. The ventricle is filled and emptied alternately as is the normal heart, the artificial valves replacing the heart-valves, which are often necessarily rendered useless by the introduction of the cannula and are at best less certain in their action than the artificial valve. The changes in the volume of the heart are shown by the movements of a liquid column in a

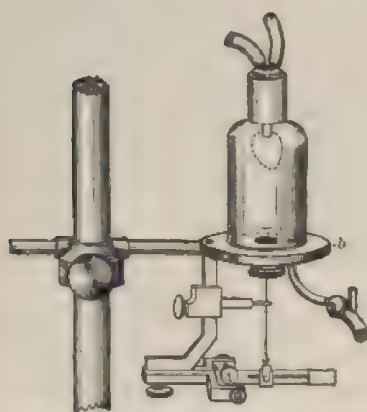


FIG. 42.—Roy's apparatus: the heart is tied on a perfusion cannula and enclosed in a bell glass resting on a brass plate, *b*, the centre of which presents an opening covered by a rubber membrane. Variations in the volume of the heart cause the membrane to rise and fall. The movements of the membrane are recorded by a lever.

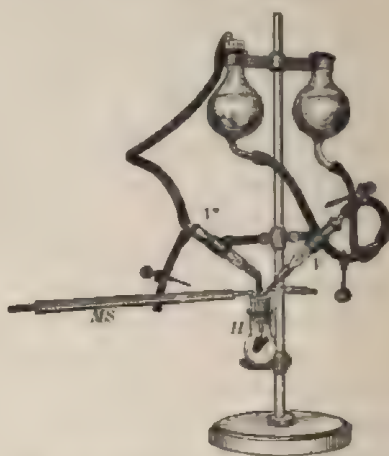


FIG. 43.—Williams's apparatus: *H*, frog's heart; *V*, *V'*, Williams's valves; *MS*, millimeter scale. The apparatus is arranged to feed the heart from the reservoir into which the heart is pumping.

horizontal tube which communicates with the bottle filled with "nutrient" fluid in which the heart is enclosed.

In the original method of Cyon the ventricle is left in connection with the auricle, the ganglion-cells of the ventricle and the neighboring portions of the auricle being kept intact. This "whole heart" preparation is to be distinguished from the "apex" preparation of Bowditch, which has also been used in studies of the effects of nutrient solutions on the heart. In Bowditch's "apex" preparation, the ventricle is bound to the cannula by a thread tied at the junction of the upper and middle thirds of the ventricle. By this means the lower two-thirds of the ventricle, which contains no ganglion-cells, is cut off from any physiological connection with the base of the ventricle and a "ganglion-free apex" secured. The isolated "apex" at first stands still, but after from ten to sixty minutes commences to beat again and can then be kept beating for several hours.

In the use of these various methods certain general precautions should be kept in mind. Special attention should be directed to the difficulty of removing the blood from the capillary fissures in the wall of the frog's heart. A small amount of blood remaining in these passages is frequently a source of error. It should be remembered that, as Cyon pointed out, a change in the nutrient solution is of itself a stimulus to the heart, increasing or diminishing the frequency of contraction and obliging the investigator to wait until the heart



has become accustomed to the new solution before making an observation. The heart should, as a rule, be constantly supplied with fresh fluid, as in the natural state. The resistance against which the heart works is also a factor of importance. The water with which the solutions are made should be distilled in glass, as the minutest trace of the compounds of heavy metals in non-colloidal solutions affects the heart.<sup>1</sup>

**Nutrient Solutions.**—Cyon found that the beat of the extirpated frog's heart is very dependent on the nature of the solution with which the heart is fed. Hearts supplied with normal saline solution (NaCl, 0.6 per cent.) ceased to beat much sooner than those left empty. The serum of dog's blood seemed almost poisonous. Rabbit's serum, on the contrary, postponed the exhaustion of the heart for many hours, provided the limited quantity contained in the apparatus was renewed from time to time. Serum used over and over again caused the beats to lose force after an hour or two. The renewal of the serum seemed a stimulus to the heart, causing it to contract very strongly during a half minute or more, after which the contractions became less energetic.

Cyon's immediate successors, Bowditch, Luciani, and Rossbach, confirmed his observations. None of these investigators, however, was concerned primarily with the nutrition of the heart. The first systematic work on this subject was done, as has been said, by Merunowicz, who attempted to maintain the beat of the heart with normal saline solution containing various quantities of blood, with normal saline alone, with a watery solution of the ash of an alcoholic extract of serum, and with a normal saline solution containing a minute amount of sodium carbonate. The direction taken by him has been pursued to the present day, the chief objects of study being the importance to the heart of sodium carbonate or other alkali, sodium and potassium chloride, the salts of calcium, oxygen, proteids and some other organic bodies such as dextrose, and, finally, of fluids possessing the physical characteristics of the blood. The outcome of this work we must now consider.

The value of an alkaline *reaction* has been generally recognized. Sodium carbonate is the alkali commonly preferred. The favorable influence of this salt probably does not depend on any specific action, but simply upon its alkalinity. The alkali promotes the beat of the heart by neutralizing the carbon dioxide and other acids formed in the metabolism of the contracting muscle; this, however, may not be its only use.

Certain of the salts normally present in the blood are necessary to maintain the beat of the heart. *Sodium chloride* is one of these. The solution employed should contain a "physiological quantity." Such a solution is said to be "isotonic." The amount required to make a sodium chloride solution "normal" or "isotonic" for the frog is 0.6 per cent., for the mammal nearly 1 per cent. Enough of a *calcium* salt to prevent the washing out of lime from the tissues is also essential for prolonged maintenance of the contractions. A heart fed with normal saline solution is before long brought to a stand; the addition of a calcium salt to the solution postpones the arrest. The character

<sup>1</sup> Locke: *Journal of Physiology*, 1895, xviii. p. 331.

of the contraction, however, is altered by the calcium, the relaxation of the ventricle being sometimes so much delayed that the next contraction takes place before the relaxation from the previous contraction has commenced, the ventricle falling thereby into a state of persistent or "tonic" contraction. The addition of a *potassium* salt restores the normal character of the contraction, calcium and potassium having an antagonistic action on the heart.<sup>1</sup> The importance of calcium to the heart is said to be demonstrated by the disappearance of the spontaneous contractions of the heart which follows the precipitation of the calcium in the circulating fluid by the addition to it of an equivalent quantity of a soluble oxalate, and by the return of spontaneous contractions which is seen when the calcium is restored to the solution.

The antagonistic action of calcium and the oxalates was first pointed out by Cyon.

According to Ringer, the substances thus far mentioned are effective in the following order: normal saline is the least effective; next is saline containing sodium bicarbonate; then saline containing tricalcium phosphate; and best of all, saline containing tricalcium phosphate together with potassium chloride. He recommends the following mixture: Sodium chloride solution 0.6 per cent., saturated with tribasic calcium phosphate, 100 cubic centimeters; solution potassium chloride 1 per cent., or acid potassium phosphate ( $\text{HK}_2\text{PO}_4$ ) 1 per cent., 2 cubic centimeters.<sup>2</sup>

There has been considerable dispute over the part played by *oxygen* in the beat of the frog's heart. McGuire and Klug were of opinion that the beat is largely independent of the amount of oxygen in the circulating fluid. Yeo concluded that the contracting heart uses more oxygen than the resting heart, and that the consumption of oxygen increases with the work done. Kronecker and Handler, on the contrary, believe that the oxygen consumption is increased by an increase in the rate of beat, but is independent of the work done. More recent observers are united on the necessity of oxygen to the working heart. Oelrwall's studies in this field are especially interesting. He finds that a volume of blood sufficient to fill the frog's ventricle will maintain contractions for hours provided the heart is surrounded by an atmosphere of oxygen. The heart is brought to a stand by lack of oxygen and may be made to beat again, even after an arrest of twenty minutes, by giving it a fresh supply. The heart fails in oxygen-hunger probably because the chemical process by which the stimulus to contraction is called forth no longer takes place, and not because of a failure in contractility, for even after long inaction a gentle touch on the pericardium will cause a vigorous contraction.<sup>3</sup>

Haldane<sup>4</sup> discovered that the corpuscles of the blood are not essential to the contractions of the warm-blooded heart, provided the oxygen which the

<sup>1</sup> Bottazzi: *Archives de Physiologie*, 1896, xxviii. p. 882.

<sup>2</sup> Ringer: *Journal of Physiology*, 1893, xiv. p. 128. The bibliography has recently been given by Howell: *American Journal of Physiology*, 1898, ii. p. 47; and Greene: *Ibid.*, p. 82; consult also White: *Journal of Physiology*, 1896, xix. p. 344.

<sup>3</sup> Oelrwall: *Skandinavisches Archiv für Physiologie*, 1898, viii. p. 1.

<sup>4</sup> Haldane: *Journal of Physiology*, 1895, xviii. p. 211.



heart needs is supplied by increasing the tension of the gas in the plasma. Haldane kept his animals alive in oxygen at a pressure of two atmospheres after the oxygen-carrying function of the red corpuscles had been destroyed with carbon monoxide. The experiment has been repeated with the extirpated mammalian heart by Porter,<sup>1</sup> Locke,<sup>2</sup> and Rusch.<sup>3</sup> Serum and even saline solutions will serve, if the oxygen tension is high or if the volume of oxygen reaching the tissues is increased simply by causing the nutrient liquid to circulate more rapidly.

*Carbon dioxide*<sup>4</sup> is injurious to the heart when present in the circulating fluid in considerable quantities. The force of the contraction is reduced before the rate of beat. The heart poisoned with carbon dioxide often falls into irregular contractions, exhibiting at times "grouping" and the "staircase" phenomenon, a series of beats regularly increasing in strength.

*Organic Substances.*—An unsuccessful effort has been made to prove that only solutions containing proteids, for example blood-serum, chyle, and milk, can keep the heart active. Recent observers have shown the incorrectness of this claim. A mixture of the inorganic salts, sodium chloride, potassium chloride, and calcium chloride, alone suffices. Locke<sup>5</sup> found that the addition of 0.1 per cent. of dextrose to a suitable inorganic solution kept a frog's heart working under a load of 3.5 centigrams, and under an "after-load" of 3 centigrams in spontaneous activity for more than twenty-four hours. The sustaining action which dextrose appears to exercise is shared, according to him, by various other organic substances.

*Physical Characteristics.*—Heffter and Albanese,<sup>6</sup> having observed that the addition of gum-arabic to the circulating fluid was of advantage, declared that the nutrient solutions should possess the viscosity of the blood. The favorable action of gum-arabic may, however, more probably be ascribed to the compounds which it contains rather than to its physical properties.<sup>7</sup>

**Mammalian Heart.**—The success attained within the past two years in the isolation of the mammalian heart opens up an hitherto unexplored region in which systematic investigation will surely bring to light facts of wide interest and value. At present, however, little is known as to the constituents of the blood which are essential to the life of the mammalian heart. An abundant supply of oxygen is certainly highly important.<sup>8</sup>

<sup>1</sup> Porter: *American Journal of Physiology*, 1898, i. p. 511.

<sup>2</sup> Locke: *Centralblatt für Physiologie*, 1898, xii. p. 568.

<sup>3</sup> Rusch: *Archiv für die gesamte Physiologie*, 1898, lxxiii. p. 535.

<sup>4</sup> Langendorff: *Archiv für Physiologie*, 1893, p. 417; *Ibid.*, p. 492; Oehrwald: *Skandinavisches Archiv für Physiologie*, 1897, vii. p. 222.

<sup>5</sup> Locke: *Journal of Physiology*, 1896, xviii. p. 332.

<sup>6</sup> Albanese: *Archiv für experimentelle Pathologie und Pharmacologie*, 1893, xxii. p. 311, *Archives italiennes de Biologie*, 1896, xxv. p. 308.

<sup>7</sup> Howell and Cooke: *Journal of Physiology*, 1893, xiv. p. 216.

<sup>8</sup> Literature is given by Magrath and Kennedy: *Journal of Experimental Medicine*, 1897, ii. p. 13; and Hedbom: *Skandinavisches Archiv für Physiologie*, 1898, vii. p. 147. See also Hering: *Archiv für die gesamte Physiologie*, 1898, lxxii. p. 163; Boek: *Archiv für experimentelle Pathologie und Pharmacologie*, 1898, xli. p. 158; and Cleghorn: *American Journal of Physiology*, 1899, ii. p. 273.



**Blood of Various Animals.**—Roy gives some data as to the effect on the frog's ventricle of the blood of various animals. The blood of the various herbivora (rabbit, guinea-pig, horse, cow, calf, sheep), as well as that of the pigeon, were found to have nearly the same nutritive value in each case. That of the dog, of the cat, and more especially of the pig, while in some instances equal in effect to that from the horse or rabbit, were in other examples (from the newly killed animals) apparently almost poisonous. Cyon's early observation of the injurious action of dog's blood on the frog's ventricle has already been mentioned!

Regarding the mammalian heart, experience has shown that it is best to supply the heart with blood from the same species of animal. The difficulties attending the use of blood from a different species are seen in the case of the dog's heart supplied with calf's blood. The heart dies sooner; oedema of the lungs takes place, impeding the pulmonary circulation and leading to engorgement of the right heart and paralysis of the right auricle; exudation into the pericardium often seriously interferes with the beat of the heart; and, finally, the elastic modulus of the cardiac muscle is apparently altered, permitting the heart to swell until it tightly fills the pericardium, when the proper filling of the heart is no longer possible through lack of room for diastolic expansion.

#### PART IV.—THE INNERVATION OF THE BLOOD-VESSELS.<sup>1</sup>

About the middle of the eighteenth century more or less sagacious hypotheses concerning the contractility of the blood-vessels began to appear in medical literature, but it was not until Henle demonstrated the existence of muscular elements in the middle coats of the arteries in 1840 that a secure foundation was laid for the present knowledge of the mechanism by which that contractility is made to control the distribution of the blood. More than a hundred years before, indeed, Pourfour du Petit had shown that redness of the conjunctiva was one of the consequences of the section of the cervical sympathetic, but had called the process an inflammation, in which false idea he was supported by Cruikshank and others; and Dupuy of Alfort had noted redness of the conjunctiva, increased warmth of the forehead, and sweat-drops on ears, forehead, and neck following his extirpation of the superior cervical ganglia in the horse; Brachet, also, cutting the cervical sympathetic in the dog, had gone so far as to attribute the resulting congestion to a paralysis of the blood-vessels. But these were merely clever speculations, for the anatomical basis necessary for a real knowledge of this subject was wanting as yet. Henle furnished this basis, and at the same time reached the modern point of view. "The part taken by the contractility of the heart and the blood-vessels in the circulation," said Henle, "can be expressed in two words: the movement of the blood depends on the heart, but its distribution depends on the vessels." Nor did Henle stop here. It was now known that the vessels possessed contractile walls; it was

<sup>1</sup> See also Bardier: *Comptes rendus Société de Biologie*, 1898, p. 548.

<sup>2</sup> See footnote to Part II., p. 148.

known further that these walls contracted when mechanically stimulated; for example, by scraping them with the point of a scalpel; and various observers had traced sympathetic nerves from the greater vessels to the lesser until lost in their finest ramifications. It was therefore easy to construct a reasonable hypothesis of the control of the blood-vessels by the nerves. Henle declared that the vessels contract because their nerves are stimulated, either directly, or reflexly through the agency of a sensory apparatus. The ground was thus prepared for the physiological demonstration of the existence of "vaso-motor" nerves, as Stilling began to call them. Four names are associated with this great achievement—Schiff, Bernard, Brown-Séquard, and Waller, each of whom worked independently of the others. Foremost among them is Claude Bernard, though not the first in point of time, for it was he who put the new doctrine on a firm basis. In his first publication Bernard stated that section of the cervical sympathetic, or removal of the superior cervical ganglion, in the rabbit, causes a more active circulation on the corresponding side of the face together with an increase in its temperature. The greater blood-supply manifests itself in the increased redness of the skin, particularly noticeable in the skin of the ear. The elevation of temperature may be easily felt by the hand. A thermometer placed in the nostril or in the ear of the operated side shows a rise of from  $4^{\circ}$  to  $6^{\circ}$  C. The elevation of temperature may persist for several months. Similar results are obtained in the horse and the dog.

The following year Brown-Séquard announced that "if galvanism is applied to the superior portion of the sympathetic after it has been cut in the neck, the dilated vessels of the face and of the ear after a certain time begin to contract; their contraction increases slowly, but at last it is evident that they resume their normal condition, if they are not even smaller. Then the temperature diminishes in the face and the ear, and becomes in the palsied side the same as in the sound side. When the galvanic current ceases to act, the vessels begin to dilate again, and all the phenomena discovered by Dr. Bernard reappear." Brown-Séquard concludes that "the only direct effect of the section of the cervical part of the sympathetic is the paralysis, and consequently the dilatation, of the blood-vessels. Another evident conclusion is that the cervical sympathetic sends motor fibres to many of the blood-vessels of the head."

While Brown-Séquard was making these important investigations in America, Bernard, in Paris, quite unaware of Brown-Séquard's labors, was reaching the same result. The existence of nerve-fibres the stimulation of which causes constriction of the blood-vessels to which they are distributed was thus established.

A considerable addition to this knowledge was presently made by Schiff, who pointed out in 1856 that certain vaso-motor nerves take origin from the spinal cord. The destruction of certain parts of the spinal cord causes the same vascular dilatation and rise of temperature that follows the section of the vaso-motor nerves outside the spinal cord.

At this time Schiff also offered evidence of vaso-dilator nerves. When



the left cervical sympathetic is cut in a dog, and the animal is kept in his kennel, the left ear will always be found to be  $5^{\circ}$  to  $9^{\circ}$  warmer than the right. If the dog is now taken out for a run in the warm sunshine, and allowed to heat himself until he begins to pant with outstretched tongue, the temperature of both ears will be found to have increased. The right ear is now, however, the warmer of the two, being from  $1^{\circ}$  to  $5^{\circ}$  warmer than the left. The blood-vessels of the right ear are, moreover, now fuller than those of the left. When the animal is quiet again the former condition returns, the redness and warmth in the right becoming again less than in the left ear. The increase of the redness and warmth of the right ear over the left, in which the vaso-constrictor nerves were paralyzed, must be the result of a dilatation of the vessels of the right ear by some nervous mechanism. For if the dilatation of the vessels was merely passive, the vessels in the right ear could not dilate to a greater degree than those in the left ear which had been left in a passive state by the section of their nerves. This experiment, however, is by no means conclusive.

The existence of vaso-dilator fibres was placed beyond doubt by the following experiment of Bernard on the chorda tympani nerve, new facts regarding the vaso-constrictor nerves being also secured. Bernard exposed the submaxillary gland of a digesting dog, removed the digastric muscle, isolated the nerves going to the gland, introduced a tube into the duct, and, finally, sought out and opened the submaxillary vein. The blood contained in the vein was dark. The nerve-branch coming to the gland from the sympathetic was now ligated, whereupon the venous blood from the gland grew red and flowed more abundantly; no saliva was excreted. The sympathetic nerve was now stimulated between the ligature and the gland. At this the blood in the vein became dark again, flowed in less abundance and finally stopped entirely. On allowing the animal to rest the venous blood grew red once more. The chorda tympani nerve, coming from the lingual nerve, was now ligated, and the end in connection with the gland stimulated. Then almost at once saliva streamed into the duct, and large quantities of bright scarlet blood flowed from the vein in jets, synchronous with the pulse.

This experiment may be said to close the earlier history of the vaso-motor nerves. It was now established beyond question that the size of the blood-vessels, and thus the quantity of blood carried by them to different parts of the body, is controlled by nerves which when stimulated either narrow the blood vessels (vaso-constrictor nerves) and thus diminish the quantity of blood that flows through them, or dilate the vessels (vaso-dilator nerves) and increase the flow. The section of vaso-constrictor nerves, for example those found in the cervical sympathetic, causes the vessels previously constricted by them to dilate. The section of a vaso-dilator nerve, for example the chorda tympani, running from the lingual nerve to the submaxillary gland, does not, however, cause the constriction of the vessels to which it is distributed. And finally, it was now determined that vaso-motor fibres are found in the sympathetic system as well as in the spinal cord and the cerebro-spinal nerves.



It remained for a later day to show that vaso-motor nerves are present in the veins as well as in the arteries. Mall has found that when the aorta is compressed below the left subclavian artery, the portal vein receives no more blood from the arteries of the intestine, yet remains for a time moderately full, because it cannot immediately empty its contents through the portal capillaries of the liver against the resistance which they offer. If the peripheral end of the cut splanchnic nerve is now stimulated, the portal vein contracts visibly and may be almost wholly emptied. Thompson<sup>1</sup> has extended the discovery of Mall to the superficial veins of the extremities. He finds that the stimulation of the peripheral end of the cut sciatic nerve, the crural artery being tied, causes the constriction of the superficial veins of the hind limb. The contraction begins soon after the commencement of the stimulation, and usually goes so far as to obliterate the lumen of the vein. Often the contraction begins nearer the proximal portion of the vein and advances toward the periphery. More commonly, however, it is limited to band-like constrictions between which the vein is filled with blood. After stimulation ceases the constrictions gradually disappear. A second and third stimulation produce much less constriction. The superficial veins of the rabbit's abdomen are constricted by the stimulation of the cervical spinal cord at the second vertebra.

The observations of Bernard and his contemporaries led to a very great number of researches on the general properties and the distribution of the vaso-motor nerves, in the course of which a variety of ingenious methods of observation have been devised.

**Methods of Observation.**—One fruitful method of research has been already incidentally mentioned, namely, the direct inspection of the vessel, or region, the vaso-motor nerves of which are being studied.

A second method consists in accurately measuring the outflow from the vein. If the blood-vessels of the area drained by the vein are constricted by the stimulation of a vaso-motor nerve, the quantity escaping from the vein in a given period previous to constriction will be greater than that escaping in an equal period during constriction. This well-known method is especially available where an artificial circulation is kept up through the organ studied, as the blood drained from the vein does not then weaken the animal and thus disturb the accuracy of the observations.<sup>2</sup>

A third method is founded on the principle in hydraulics that the lateral pressure at any point in a tube through which a liquid flows depends, other things being equal, on the resistance to be overcome below the point at which the pressure is measured. In the animal body the resistance to be overcome by the blood-stream varies with the state of contraction of the smaller vessels, and thus the variations in the lateral pressure of a given artery may, under certain restrictions, be used to determine variations in the size of the smaller

<sup>1</sup> Thompson: *Archiv für Physiologie*, 1893, p. 104; Bancroft: *American Journal of Physiology*, 1898, i. p. 477.

<sup>2</sup> Cavazzani and Manca: *Archives italiennes de Biologie*, 1895, xxiv. p. 33.

vessels distal to the artery. The restrictions are, that the variations in the lateral pressure in the artery are indicative of changes in the size of the distal vessels only when the general blood-pressure remains unaltered, or alters in a direction opposite to the change in the artery investigated. An example will make this plain. Dastre and Morat, in order to demonstrate the presence of vaso-motor fibres for the hind limb in the sciatic nerve, connected a manometer with the central end of the left femoral artery, and a second manometer with the peripheral end of the right femoral artery, distal to the origin of the profunda femoris. The anastomoses between the principal branches of the femoral artery are so numerous and so large that the circulation in the limb can be maintained by the profunda femoris alone. Dastre and Morat could therefore compare the general blood-pressure with the blood-pressure in the right hind limb. On stimulating the peripheral end of the right sciatic nerve, the blood-pressure rose in the arteries of the limb, but remained stationary in the arteries of the trunk, connected with the first manometer through the central end of the left femoral artery. The rise of blood-pressure in the operated limb, while the blood-pressure in the rest of the body remained unchanged, proved that the vessels in the operated limb were constricted.

Many investigators have studied vaso-motor phenomena by means of the plethysmograph, an apparatus invented by Mosso for recording the changes in the volume of the extremities. The member, the vaso-motor nerves of which are to be studied, is placed within a cylinder filled with water, from which a tube leads to a recording tambour. An increase in the volume of the member, such as would be brought about by the expansion of its vessels, causes a corresponding volume of water to enter the tambour tube, thus raising the pressure in the tambour and forcing its lever to rise. A constriction of the vessels, on the contrary, causes the recording lever to fall.

In addition to these general methods, special devices have been employed in the researches into the vaso-motor nerves of the brain.

In considering the observations made with these various methods it will be advisable to begin with the differences between the two kinds of vaso-motor nerves.

**Differences between Vaso-constrictor and Vaso-dilator Nerves.**—The differences between vaso-constrictor and vaso-dilator nerves are particularly interesting for the reason that both vaso-constrictor and vaso-dilator fibres are often found in one and the same anatomical nerve. The sciatic nerve is a good example of this. By taking advantage of these differences the investigator may determine whether one or both kinds of fibres are present in any anatomical nerve; whereas, without this knowledge, the effects produced by the stimulation of the one might be wholly masked by the effects produced by the stimulation of the other.

The vaso-constrictors are less easily excited than the vaso-dilators. The simultaneous and equal stimulation of the dilator and constrictor nerves going to the submaxillary gland causes vaso-constriction, dilatation appearing after the stimulation ceases, for the after-effect of excitation is of shorter duration



with the constrictors than with the dilators. Warming increases and cooling diminishes the excitability of the vaso-constrictors to a greater degree than is the case with the vaso-dilators. Thus if the hind limb of an animal be warmed, the stimulation of the sciatic nerve will cause vaso-constriction; while if it be cooled the same stimulation will cause vaso-dilatation.<sup>1</sup> Vaso-constrictors are more sensitive to rapidly repeated induction shocks (tetanization) and less sensitive to single induction shocks than are vaso-dilators. Thus if the sciatic nerve is stimulated with induction shocks of the same strength, it will be found that a rapid repetition of the stimuli will give vaso-constriction, while with single shocks at intervals of five seconds vaso-dilatation is the result. Vaso-constrictors degenerate more rapidly than vaso-dilators after separation from their cells of origin. The stimulation of the peripheral end of the frog's sciatic nerve immediately after section causes constriction. Several days later the same stimulation causes vaso-dilatation, the constrictor nerves having already degenerated (see Fig. 44, *B*). The maximum effect of stimulation is more quickly reached with the vaso-constrictor than with the vaso-dilator nerves. There is also a difference in the latent period, or interval between stimulation

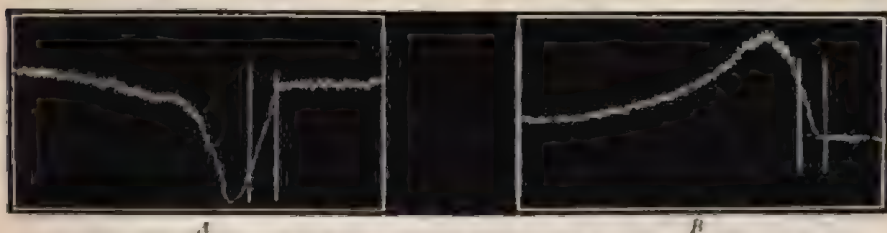


FIG. 44.—Curves obtained by enclosing the hind limb of a cat in the plethysmograph and stimulating the peripheral end of the cut sciatic nerve (Bowditch and Warren, 1888, p. 447). The curves read from right to left. In each case the vertical lines show the duration of the stimulus—namely, fifteen induction shocks per second during twenty seconds. Curve *A* shows the contraction of the vessels produced by the excitation of the freshly-divided nerve; curve *B*, the dilatation produced by an equal excitation of the nerve of the opposite side four days after section, the vaso-constrictor nerves having degenerated more rapidly than the vaso-dilators.

and response. Bowditch and Warren have found the latent period of the vaso-constrictor fibres in the sciatic to be about 1.5 seconds, while that of the vaso-dilators is 3.5 seconds. Finally, the two sorts of nerves have been said to differ in the manner in which they are distributed. The vaso-constrictor nerves leave the cord as medullated fibres, enter the sympathetic chain of ganglia and end in terminal branches probably in contact with a sympathetic ganglion-cell. The constrictor impulse is forwarded to the vessel by a process of this cell, either directly or by means of still other sympathetic ganglion-cells. The vaso-dilator fibre, on the contrary, was thought to run directly from the cord to the blood-vessel; but recent investigations make it probable that all spinal vaso-motor fibres end in sympathetic ganglia.

**Origin and Course.**—The vaso-motor nerves the general properties of which have just been studied are axis-cylinder processes of sympathetic ganglion-cells. They follow, for a time at least, the course of the corresponding

<sup>1</sup> Howell, Budgett, and Leonard: *Journal of Physiology*, 1894, xvi, p. 298.



spinal nerve. According to Langley,<sup>1</sup> they do not differ from the vaso-motor and secretory nerves except in the nature of the structure in which they terminate. They are not interrupted by other nerve-cells on their course. The action of the sympathetic vaso-motor cells is influenced by the vaso-motor cells of the spinal cord and bulb. These are probably small cells situated at various levels in the anterior horn and lateral gray substance. Their axis-cylinder processes leave the cerebro-spinal axis by the anterior roots<sup>2</sup> of certain spinal and by certain cranial nerves, and enter sympathetic ganglia, where they end in terminal twigs probably in contact with the sympathetic vaso-motor cells. The vaso-motor cells lying at various levels in the cerebro-spinal axis are in turn largely controlled by an association of cells situated in the bulb and termed the vaso-motor centre. The neuraxons (axis-cylinder processes) of the cells composing this "centre" pass in part to the nuclei of certain cranial nerves and in part down the lateral columns of the cord, to end in contact with the spinal vaso-motor cells. The vaso-motor apparatus consists, then, of three classes of nerve-cells.<sup>3</sup> The cell-bodies of the first class lie in sympathetic ganglia, their neuraxons passing directly to the smooth muscles in the walls of the vessels; the second are situated at different levels in the cerebro-spinal axis, their neuraxons passing thence to the sympathetic ganglia by way of the spinal and cranial nerves; and the third are placed in the bulb and control the second through intraspinal and intracranial paths. The nerve-cell of the first class lies wholly without the cerebro-spinal axis, the third wholly within it, while the second is partly within and partly without, and binds together the remaining two.

The evidence for the existence of these vaso-motor nerve-cells must now be considered. We shall begin with those of the third class, constituting the so-called bulbar vaso-motor centre.

**Bulbar Vaso-motor Centre.**—The section of the spinal cord near its junction with the bulb is followed by the general dilatation of the blood-vessels of the trunk and limbs. The dilated vessels are again constricted when the severed fibres in the spinal cord are artificially stimulated. Hence the section caused the dilatation by interrupting the vaso-constrictor impulses passing from the bulb to parts below. The position of the bulbar vaso-constrictor centre has been determined by Owsjannikow and Dittmar. The former observer divided the bulb transversely at various levels. When the section fell immediately caudal to the corpora quadrigemina, only a slight temporary rise in blood-pressure was observed. When, however, the section fell a millimeter or two nearer the cord, a considerable and permanent fall in the blood-pressure was noted. Further lowering was seen as the sections were carried still farther toward the spinal cord, until at length, about four millimeters from the corpora quadrigemina, no further fall took place. The

<sup>1</sup> Langley: *Journal of Physiology*, 1894, xvii. p. 314.

<sup>2</sup> Compare Werzloff. *Centralblatt für Physiologie*, 1896, x. p. 194.

<sup>3</sup> By "nerve-cells" is meant the cell-body with all its processes, namely, the neuraxon, or axis-cylinder process, and the dendrites, or protoplasmic processes.

area from which the vaso-constrictor nerves receive a constant excitation extends, therefore, in the rabbit, over about three millimeters of the bulb not far from the corpora quadrigemina. Two years after this investigation Dittmar added to the observations of Owsjannikow the fact that the vaso-constrictor centre is bilateral, lying in the anterior part of the lateral columns on both sides of the median line. At this site is found a group of ganglion-cells known as the antero-lateral nucleus of Clarke. It is possible, though far from certain, that these are the cells of the vaso-constrictor centre.

The vaso-constrictor centre in the bulb is always in a state of action, or "tonic" excitation, as is shown by the dilatation of the vessels when deprived of their constrictor impulses through the section of the spinal cord.

It is not definitely known whether a vaso-dilator centre is present in the bulb.

**Spinal Centres.**—A complete demonstration of the existence of vaso-motor centres in the spinal cord, first suggested by Marshall Hall, was made by Goltz and Freusberg in their experiments on dogs which had been kept alive after the division of the spinal cord at the junction of the dorsal and the lumbar regions. This operation cuts off both sensory and motor communication between the parts lying above and below the plane of section, and divides the animal physiologically into a fore dog and a hind dog, to use the author's expression. The investigator can now explore the lumbar cord unvexed by cerebral impulses. A great number of motor reflexes formerly thought to have their centres exclusively in the brain are by this means found to take place in the absence of the brain.<sup>1</sup> That vaso-motor reflexes were among them was discovered by accident. It was noticed that the mechanical stimulation of the skin of the abdomen and penis while the animal was being washed provoked erection, which, as Eckhard had discovered some years before, is a reflex action due to the dilatation of the arteries of the penis through impulses conveyed by the *nervi erigentes*. Pressure on the bladder, or the walls of the rectum, also had this effect. After the destruction of the lumbar cord this reflex was no longer possible. The vessels of the hind limb are also connected with vaso-motor cells in the lumbar cord. Soon after the section of the cord in the dorsal region the hind paws are observed to be warmer than the fore paws, and the arteries of the hind limb are seen to beat more strongly. This is the result of cutting off the vaso-constrictor impulses from the bulbar centre to the vessels in question. If the animal survives a considerable time the hind paws will be observed to grow cooler from day to day until they are again no warmer than the fore paws. Destruction of the lumbar cord now causes the temperature of the hind limbs to rise again.

The conclusion drawn from these observations is that vaso-motor cells are present in the spinal cord. It is probable that they are normally subordinated to the bulbar nerve-cells and require a certain time after separation from the bulb in order to develop their previously rudimentary powers. Hence the

<sup>1</sup> Later experiments by Goltz and Ewald, showing the degree of independence of the spinal cord possessed by sympathetic vaso-motor neurons, will presently be cited.



interval of many days between the section and the return of arterial tone in areas distal to the section. It has been suggested that during this period the power of the spinal nerve-cell is inhibited by impulses proceeding from the cut surface of the cord,<sup>1</sup> but this long inhibition is questionable in view of the fact that transverse section of the cord in rabbits and dogs does not inhibit the phrenic nuclei.<sup>2</sup>

The spinal nerve-cell takes part in vaso-motor reflexes. Thus the stimulation of the central end of the brachial nerves after section of the spinal cord at the third vertebra causes a dilatation of the vessels of the fore limb. The stimulation of the central end of the sciatic nerve after the division of the spinal cord causes a general rise of blood-pressure indicating the constriction of many vessels. The sensory stimulation of one hind limb may cause reflexly a narrowing of the vessels in the other, after the spinal cord is severed in the mid-thoracic region. In asphyxia, after the separation of the cord from the brain, vascular constriction is produced reflexly through the spinal centres. This constriction is not observed if the cord is previously destroyed. Goltz and Ewald find that the tonic constriction of the vessels of the hind limbs returns after the extirpation of the lower part of the spinal cord.

**Sympathetic Vaso-motor Centres.**—Gley<sup>3</sup> finds that after the destruction of both bulbar and spinal centres some degree of vascular tone is still maintained. The extraordinary experiments of Goltz and Ewald place this fact beyond question. These physiologists remove the lower part of the spinal cord completely, taking away 80 millimeters or more. For a few days after the operation the hind limbs are hot and red, from dilatation of their blood-vessels. Soon, however, the hind limbs become as cool, and sometimes even cooler, than the fore limbs, their arterial tonus being re-established and maintained without the help of the spinal cord.

The sympathetic ganglia are probably also centres of reflex vaso-motor action. The fact that these ganglia act as centres for other motor reflexes would itself suggest this possibility. Evidence of the vaso-motor reflex function of the first thoracic ganglion has been offered recently by François-Franck.<sup>4</sup> The two branches composing the annulus of Vieussens contain both afferent and efferent fibres. If one of the branches is cut, and the end in connection with the first thoracic ganglion is stimulated, the ganglion having been separated from the spinal cord by the section of the communicating branches, a constriction of the vessels of the ear, the submaxillary gland, and the nasal mucous membrane may be observed.

This evidence, together with the probability that the neuraxons of all the spinal vaso-motor cells end in sympathetic ganglia,<sup>5</sup> makes it fairly credible that the sympathetic vaso-motor nerve-cell possesses central functions.

<sup>1</sup> Goltz and Ewald: *Archiv für die gesammte Physiologie*, 1896, lxiii. p. 397.

<sup>2</sup> Porter: *Journal of Physiology*, 1895, xvii. p. 459.

<sup>3</sup> Gley: *Archives de Physiologie*, 1894, p. 704.

<sup>4</sup> Franck: *Archives de Physiologie*, 1894, p. 721.

<sup>5</sup> See the statement of Langley's results with the nicotin method on page 208.



There has been much discussion over the meaning of the rhythmic contractions observed in certain blood-vessels apparently independent of the central nervous system.<sup>1</sup> The median artery of the rabbit's ear, the arteria saphena in the same animal, and the vessels in the frog's web and frog's mesentery, slowly contract and relax. This rhythmic contraction is easily seen in the ear of a white rabbit. The movements are possibly of purely muscular origin, but are more probably the result of periodical discharges by vaso-motor nerve-cells.

*Rhythmical variations in the tonus of the vaso-constrictor centres* are often held to explain the oscillations seen in the blood-pressure curve after the influence of thoracic aspiration has been eliminated by opening the chest and cutting the vagus nerves. These oscillations are of two sorts. In the one, the blood-pressure sinks with every inspiration and rises with every expiration, though the rise and fall are not precisely synchronous with the respiratory movements; in the other, the so-called Traube-Hering waves, the oscillations embrace several respirations. It has also been suggested that these phenomena are due to periodical changes in the respiratory centre affecting the vaso-constrictor centre by "irradiation."

**Vaso-motor Reflexes.**—The vaso-motor nerves can be excited reflexly by afferent impulses conveyed either from the blood-vessels themselves or from the end-organs of sensory nerves in general. The existence of reflexes from the blood-vessels may be shown by Heger's experiment. Heger observed a rise of general blood-pressure with a subsequent fall, and at times a primary fall, after the injection of nitrate of silver into the peripheral end of the crural artery of a rabbit. The limb, with the exception of the sciatic nerve, was severed from the trunk. The quantity injected was so small that it probably was decomposed before passing the capillaries or escaping from the blood-vessels. Thus the effect exerted by the nitrate of silver on the general blood-pressure was probably caused by afferent impulses set up in the blood-vessels themselves and transmitted through the sciatic nerve to the vaso-motor centres. Vaso-motor reflexes are, however, much more commonly produced by the stimulation of sensory nerves other than those present in the blood-vessels.

The reflex constriction or dilatation<sup>2</sup> appears usually in the vascular area from which the afferent impulses arise. For example, the stimulation of the central end of the posterior auricular nerve in the rabbit causes a passing constriction followed by dilatation, or a primary dilatation often followed by constriction of the vessels in the ear. The stimulation of the nervi erigentes causes dilatation of the vessels of the penis. Gaskell found that the vessels of the mylo-hyoid muscle widened on stimulating the mucous membrane at the entrance of the glottis.

<sup>1</sup> Frauck: *Archives de Physiologie*, 1893, p. 729; Lui: *Archives italiennes de Biologie*, 1894, xxi. p. 416; Goltz and Ewald: *Archiv für die gesamte Physiologie*, 1896, lxxiii. p. 396.

<sup>2</sup> Hegglin: *Zeitschrift für klinische Medizin*, 1894, xxvi. p. 25.

The vascular reflex <sup>1</sup> may appear in a part associated in function with the sensory surface stimulated. Thus the stimulation of the tongue causes dilatation of the blood-vessels in the submaxillary gland. Frequently the vascular reflex is seen on both sides of the body. The stimulation of the mucous membrane on one side of the nose may cause vascular dilatation in the whole head; the effect in this case is usually more marked on the side stimulated. The vessels of one hand contract when the other hand is put in cold water. Sometimes distant and apparently unrelated parts are affected. Vulpian noticed that the stimulation of the central end of the sciatic caused the vessels of the tongue to contract.<sup>2</sup>

The vascular changes produced reflexly in the splanchnic area are of especial importance because of the great number of vessels innervated through these nerves and the great changes in the blood-pressure that can follow dilatation or constriction on so large a scale.

There is in some degree an inverse relation between the vessels of the skin and deeper parts on reflex stimulation of the vaso-motor centres. The superficial vessels are often dilated while those of deeper parts are constricted.<sup>3</sup> Thus the stimulation of the central end of the sciatic nerve may cause a dilatation of the vessels of the lips, hand in hand with a rise in general blood-pressure.<sup>4</sup> Exposing a loop of intestine dilates the intestinal vessels in the rabbit, but constricts those of the ear. In asphyxia, the superficial vessels of the ear, face, and extremities dilate, while the vessels of the intestine, spleen, kidneys and uterus are constricted.

**Relation of Cerebrum to Vaso-motor Centres.**—A rise of general blood-pressure has been produced by the stimulation of different regions of the cortex and of various other parts of the brain; for example, the *crura cerebri* and *corpora quadrigemina*. Vaso-dilatation has also been observed. The motor area of the cortex especially seems closely connected with the bulbar vaso-motor centres. There is, however, no conclusive evidence that special vaso-motor centres exist in the brain aside from the bulbar centres already described. At present the safer view is that the changes in blood-pressure called forth by the stimulation of various parts of the brain are reflex actions, the afferent impulse starting in the brain as it might in any other tissue peripheral to the vaso-motor centres.

**Pressor and Depressor Fibres.**—The stimulation of the same afferent nerve sometimes causes reflex dilation of the vessels of a part, instead of the more usual reflex constriction. Two explanations of this fact have been suggested. The first assumes that the condition of the vaso-motor centre varies in such a way that the same stimuli might produce contrary effects, depending on the relation between the time of stimulation and the condition of the centre.

<sup>1</sup> The general arrangement of the matter in this paragraph is that given by Tigerstedt, *Der Kreislauf*, 1893, p. 519.

<sup>2</sup> Compare Sergejew *Centralblatt für die medizinische Wissenschaft*, 1894, p. 162.

<sup>3</sup> Wertheimer: *Comptes rendus*, 1893, cxvi. p. 595; Hallion and Franck: *Archives de Physiologie*, 1896, p. 502; Bayliss and Bradford: *Journal of Physiology*, 1894, xvi. p. 17.

<sup>4</sup> Isorgin *Archiv für Physiologie*, 1894, p. 448.



The second assumes the existence of special reflex constrictor or "pressor" fibres, and reflex dilator or "depressor" fibres. The existence of at least one depressor nerve is beyond question, namely the cardiac depressor nerve, which it will be remembered runs from the heart to the bulb and when stimulated causes a dilatation of the splanchnic and other vessels reflexly through the bulbar vaso-motor centre. Evidence of other reflex vaso-dilator nerves and of reflex vaso-constrictor fibres as well has been offered by Latschenberger and Deahna, Howell,<sup>1</sup> and others. Howell, for example, has found that if a part of the sciatic nerve is cooled to near 0° C. and the central end stimulated peripherally to this part, the blood-pressure falls, instead of rising, as it does when the nerve is stimulated without previous cooling. Howell's experiments have been recently extended by Hunt, who finds that the stimulation of the sciatic during its regeneration after section gives at first vaso-dilatation only, but when regeneration has progressed still further, vaso-constriction is secured. These results point to the existence of both pressor and depressor fibres, the latter being the first to regenerate after section. A reflex fall in blood-pressure is also produced by stimulating various mixed nerves with weak currents and by the mechanical stimulation of the nerve-endings in muscle. The fall is more readily obtained when the animal is under ether, chloroform, or chloral, less readily under curare.

**Topography.**—We pass now to the vaso-motor nerves of various regions.

**Brain.**<sup>2</sup>—The study of the innervation of the intracranial vessels is rendered exceptionally difficult by the fact that the brain and its blood-vessels are placed in a closed cavity surrounded by walls of unyielding bone. The fundamental difference created by this arrangement between the vascular phenomena of the brain and those of other organs was recognized in part at least by the younger Monro as long ago as 1783. Monro declared that the quantity of blood within the cranium is almost invariable, "for, being enclosed in a case of bone, the blood must be continually flowing out of the veins that room may be given to the blood which is entering by the arteries,—as the substance of the brain, like that of the other solids of our body, is nearly incompressible." Further differences between the circulation in the brain and in other organs are introduced by the presence of the cerebro-spinal fluid in the ventricles and in the arachnoidal spaces at the base of the brain. This fluid may pass out into the spinal canal and thus leave room for an increase in the amount of blood in the cranium. Finally, a rise of pressure in the arteries too great to be compensated by the outflow of cerebro-spinal fluid may lead to compression of the venous sinuses and a decided change in the relative distribution of the blood in the arteries, capillaries and veins—conditions which are not present in extracranial tissues. It is evident, therefore, that the methods employed in the search for vaso-motor nerves within the cranium must take

<sup>1</sup> Howell, Budgett, and Leonard: *Journal of Physiology*, 1894, xvi. p. 310; Bayliss: *Ibid.*, 1893, xiv. p. 317; Bradford and Dean: *Ibid.*, 1894, xvi. p. 67; Hunt: *Ibid.*, 1895, xviii. p. 381.

<sup>2</sup> Cavazzani: *Archives italiennes de Biologie*, 1893, xviii. p. 54, xix. p. 214; Bayliss and Hill: *Journal of Physiology*, 1895, xviii. p. 334; Gulland: *Ibid.*, p. 361.



into account many sources of error that are absent in vaso-motor studies of other regions. It is, indeed, probable that incompleteness of method will go far toward explaining the disagreement of authors as to the presence of vaso-motor nerves in the brain. According to Bayliss and Hill, who have recently studied this subject, it is necessary to record simultaneously the arterial pressure, the general venous pressure, the intracranial pressure and the cerebral venous pressure, the cranium as in the normal condition being kept a closed cavity. In their experiments, "a cannula was placed in the central end of the carotid artery. A second long cannula was passed down the external jugular vein, and on the same side, into the right auricle. The torcular Herophili was trephined, and a third cannula, this time of brass, was screwed into the hole thus made." The intracranial pressure was recorded by a cannula connected through another trephine-hole with the subdural space.

Bayliss and Hill could find no evidence of the existence of cerebral vaso-motor nerves. The cerebral circulation, according to them, passively follows the changes in the general arterial and venous pressure. Gulland has examined the cerebral vessels by the Golgi, Ehrlich, and other methods, to determine whether nerve-fibres could be demonstrated in them. None were found. It is probable that the blood-supply to the brain is regulated through the bulbar vaso-constrictor centre. Anæmia or asphyxia of the brain stimulates the cells composing this centre, vascular constriction of many vessels follows, and more blood enters the cranial cavity. The vessels of the splanchnic area play a chief part in this regulative process.<sup>1</sup> Their importance to the circulation in the brain is shown by the fatal effect of the section of the splanchnic nerves in the rabbit. On placing the animal on its feet, so much blood flows into the relaxed abdominal vessels that death may follow from anæmia of the brain.

*Vaso-motor Nerves of Head.*—The cervical sympathetic contains vaso-constrictor fibres for the corresponding side of the face, the eye, ear, salivary glands and tongue, and possibly the brain. The spinal vaso-constrictor fibres for the vessels of the head in the cat and dog leave the cord in the first five thoracic nerves; in the rabbit, in the second to eighth thoracic, seven in all.

Vaso-dilator fibres for the face and mouth have been found in the cervical sympathetic by Dastre and Morat, leaving the cord in the second to fifth dorsal nerves, and uniting (at least for the most part) with the trigeminus by passing, according to Morat, from the superior cervical sympathetic ganglion to the ganglion of Gasser. Other dilator fibres for the skin and mucous membrane of the face and mouth arise apparently in the trigeminus, for the stimulation of this nerve between the brain and Gasser's ganglion causes dilatation of the vessels of the face,<sup>2</sup> and in the nerve of Wrisberg.

The vaso-motor nerves of the tongue have been recently studied by Isergin.<sup>3</sup>

<sup>1</sup> Wertheimer: *Archives de Physiologie*, 1893, p. 297.

<sup>2</sup> Langley: *Philosophical Transactions*, 1892, p. 104; Piotrowsky: *Centralblatt für Physiologie*, 1892, vi p. 404.

<sup>3</sup> Isergin: *Archiv für Physiologie*, 1894, p. 441.

The lingual and the glosso-pharyngeal nerves are recognized by all authors as dilators of the lingual vessels. The sympathetic and the hypoglossus contain constrictor fibres for the tongue. It is possible that the lingual contains also a small number of constrictor fibres. Most if not all these vaso-motor fibres arise in the sympathetic and reach the above-mentioned nerves by way of the superior cervical ganglion. They degenerate in from three to five weeks after the extirpation of the ganglion.

Morat and Doyon cut the cervical sympathetic in a curarized rabbit and examined the retinal arteries with the ophthalmoscope. They were found dilated. The excitation of the cervical sympathetic caused constriction, the excitation of the thoracic sympathetic dilatation of these vessels. The retinal fibres leave the sympathetic at the superior cervical ganglion and pass along the communicating ramus to the ganglion of Gasser, whence they reach the eye through the ophthalmic branch of the fifth nerve, the gray root of the ophthalmic ganglion, and the ciliary nerves. Most, or all, of the fibres for the anterior part of the eye are found in the fifth nerve.

*Lungs.*—The methods ordinarily employed for the demonstration of vaso-motor nerves cannot without danger be used in the study of the innervation

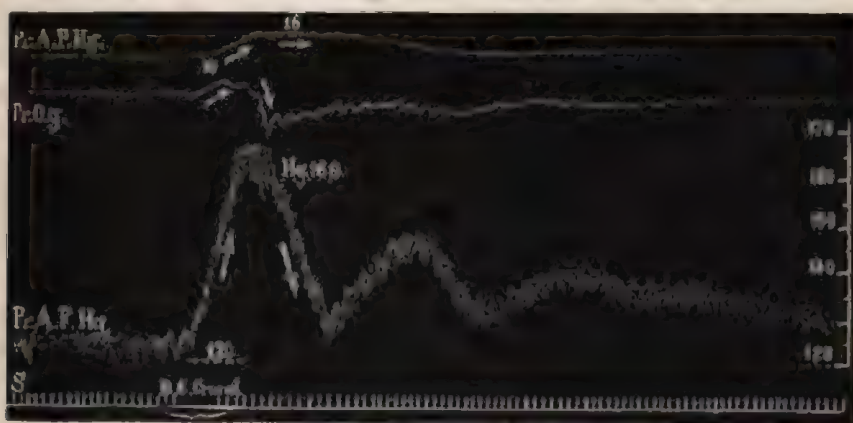


FIG. 45.—The excitation of the central end of the inguinal branch of the crural (sciatic) nerve causes a rise in the aortic pressure (*Pr A.F.*), a rise in the pressure in the pulmonary artery (*Pr A.F.*) of 10 to 16 mm. Hg., accompanied by a falling pressure in the left auricle (*Pr O.G.*) (Franck, 1896, p. 184). The rise of pressure in the pulmonary artery, together with the fall in the left auricle, demonstrate, according to Franck, a constriction of the pulmonary vessels.

of the pulmonary vessels.<sup>1</sup> A fall in the blood-pressure in the pulmonary artery, for example, produced by stimulating any nerve cannot be taken as final evidence that the stimulation caused the constriction of the pulmonary vessels. The lesser circulation is so connected that changes in the calibre of the vessels of a distant part, the liver for example, may alter the quantity of blood in the lungs. The method of Cavazzani avoids these difficulties. Cavazzani establishes an artificial circulation through one lobe of a lung in

<sup>1</sup> Doyon: *Archives de Physiologie*, 1893, p. 101; Henriques: *Skandinavische Archiv für Physiologie*, 1893, iv. p. 229; Bradford and Dean: *Journal of Physiology*, 1894, xvi. p. 34; Franck: *Archives de Physiologie*, 1896, p. 178.



a living animal, and measures the outflow per unit of time. An increase in the outflow means a dilatation of the vessels, diminution means constriction. He finds that the outflow diminishes in the rabbit when the vagus is stimulated in the neck, and increases when the cervical sympathetic is stimulated. Franck measures the pressure simultaneously in the pulmonary artery and left auricle, a method apparently also trustworthy. The stimulation of the inner surface of the aorta causes a rise of pressure in the pulmonary artery and a simultaneous fall in the left auricle, indicating, according to Franck, the vaso-constrictor power of the sympathetic nerve over the pulmonary vessels. A reflex constriction is also produced by the stimulation of the central end of a branch of the sciatic, intercostal, abdominal pneumogastric, and abdominal sympathetic nerves (see Fig. 45).

*Heart.*—Vaso-motor fibres for the coronary arteries of the heart have been described.<sup>1</sup>

*Intestines.*<sup>2</sup>—The mesenteric vessels receive vaso-constrictor fibres from the sympathetic chiefly through the splanchnic nerve. The vaso-constrictors of the jejunum, as a rule, begin to be found in the rami of the fifth dorsal nerves; a little lower down, those for the ileum come off; and still lower down, those for the colon; none arise below the second lumbar pair. According to Hallion and Franck, vaso-dilator fibres are present in the same sympathetic nerves that contain vaso-constrictors. The dilator fibres are most abundant or most powerful in the rami of the last three dorsal and first two lumbar nerves. There is some evidence of the presence of vaso-dilator fibres in the vagus. The excitation of the vaso-constrictor centres by the blood in asphyxia produces constriction of the abdominal vessels. The vaso-dilator as well as the vaso-constrictor fibres of the splanchnic probably end in the solar and renal plexuses.

*Liver.*—Cavazzani and Manca<sup>3</sup> have recently attempted to show the presence of vaso-motor fibres in the liver. Their method consists in passing warm normal saline solution from a Mariotte's flask at a pressure of 8 to 10 millimeters Hg through the hepatic branches of the portal vein and measuring the outflow in a unit of time from the ascending vena cava. On stimulating the splanchnic nerve they observed that the outflow was usually diminished though sometimes increased, indicating perhaps that the splanchnics contain both vaso-constrictor and vaso-dilator fibres for the hepatic branches of the portal vein. The vagus appeared to contain vaso-dilator fibres. Further studies are necessary, however, before pronouncing definitely upon these questions.

<sup>1</sup> Porter: *Boston Medical and Surgical Journal*, 1896, cxxxiv. 39; Porter and Beyer: *American Journal of Physiology*, 1900, iii. p. xxiv.; Maass: *Archiv für die gesammte Physiologie*, 1899, lxxiv. p. 281.

<sup>2</sup> Hallion and Franck: *Archives de Physiologie*, 1896, xxviii. pp. 478, 493; Bunch: *Journal of Physiology*, 1899, xxiv. p. 72.

<sup>3</sup> Cavazzani and Manca: *Archives italiennes de Biologie*, 1895, xxiv. p. 33; François-Franck and Hallion: *Archives de Physiologie*, 1896, pp. 908, 923; 1897, pp. 434, 448.



**Kidney.**<sup>1</sup>—The vaso-motor nerves of the kidney leave the cord from the sixth dorsal to the second lumbar nerve. In the dog, most of the renal vaso-motor fibres are found in the eleventh, twelfth, and thirteenth dorsal nerves. The stimulation of the nerves entering the hilus of the kidney between the artery and vein causes a marked and sudden renal contraction, but the organ soon regains its former volume. Constriction follows also the stimulation of the peripheral end of the cut splanchnic nerve. Bradford has demonstrated renal vaso-dilator fibres for certain nerves by stimulating at the rate of one induction shock per second. For example, the excitation of the thirteenth dorsal nerve with 50 to 5 induction shocks per second gave always a constriction of the kidney, but when a single shock per second was employed, the kidney dilated. If the cells connected with the renal vaso-motor fibres are stimulated directly by venous blood as in asphyxia, the animal being curarized, a decided constriction of the kidney results. The reflex excitation of these cells is of especial importance. The stimulation of the central end of the sciatic or the splanchnic nerves causes renal constriction. The same effect is easily produced by stimulating the skin, for example, by the application of cold. The stimulation of the sole of the foot in a curarized dog caused contraction of the renal vessels. There is some evidence that the splanchnic vaso-motor fibres for the kidney end in the cells of the renal plexus.

**Spleen.**—The stimulation of the peripheral end of the splanchnic nerves causes a sudden and large diminution in the volume of the spleen.<sup>2</sup> It is, however, not certain whether the constriction of the spleen is to be referred primarily to a constriction of its blood-vessels or to the contraction of the intrinsic muscular fibres which play so large a part in the changes of volume of this organ. The doubt is strengthened by the fact that section of the splanchnic nerves does not alter the volume of the spleen; dilatation would be expected were these nerves the pathway of vaso-constrictor fibres for the spleen.

**Pancreas.**—François-Franck and Hallion find vaso-constrictor fibres in the sympathetic chain between the sixth and eleventh ribs; they leave the spinal cord from the fifth dorsal to the second lumbar ramus communicans, pass into the greater and lesser splanchnic nerves, and reach the gland along the pancreatic artery. A few dilator fibres were found in the sympathetic; more in the the vagus.<sup>3</sup>

**External Generative Organs.**<sup>4</sup>—The recent history of the vaso-motor nerves of the external generative organs—namely, those developed from the urogenital sinus and the skin surrounding the urogenital opening—begins with Eek-

<sup>1</sup> Wertheimer *Archives de Physiologie*, 1894, p. 308; Bayliss and Bradford: *Journal of Physiology*, 1894, xvi. p. 17.

<sup>2</sup> Schäfer and Moore: *Journal of Physiology*, 1896, xx. p. 1.

<sup>3</sup> Franck and Hallion: *Archives de Physiologie*, 1896, pp. 908, 923.

<sup>4</sup> Franck: *Archives de Physiologie*, 1895, p. 122; Langley and Anderson: *Journal of Physiology*, 1895, xix. p. 76.

hard, who showed that the stimulation of certain branches of the first and second, and occasionally the third, sacral nerves (dog) caused a dilatation of the blood-vessels of the penis and erection of that organ, and with Goltz, who found an erection centre in the lumbo-sacral cord. Numerous researches in recent years, among which the reader is referred especially to the work of Langley and Langley and Anderson, have shown that the vaso-motor nerves of the external generative organs of both sexes may be divided into a lumbar and a sacral group.

The *lumbar fibres* pass out of the cord in the anterior roots of the second, third, fourth, and fifth lumbar nerves, and run in the white rami communicantes to the sympathetic chain, from which they reach the periphery either by way of the pudic nerves or by the pelvic plexus. The greater number take the former course, running down the sympathetic chain to the sacral ganglia, and passing from these ganglia through the gray rami communicantes to the sacral nerves. None of the fibres thus derived enter the *nervi erigentes* of Eckhard. Of the various branches of the pudic nerves (rabbit), the *nervus dorsalis* causes constriction of the blood-vessels of the penis and the perineal nerve contraction of the blood-vessels of the scrotum. The course by way of the pelvic plexus is taken by relatively few fibres. They run for the most part in the hypogastric nerves, a few sometimes joining the plexus from the lower lumbar or upper sacral sympathetic chain, or from the aortic plexus. The presence of vaso-dilator fibres in the lumbar group is disputed.

The *sacral group* of nerves leave the spinal cord in the sacral nerve roots. Their stimulation causes dilatation of the vessels of the penis and vulva.

*Internal Generative Organs* (those developed from the Müllerian or the Wolffian ducts).—Langley and Anderson find vaso-constrictor fibres for the Fallopian tubes, uterus, and vagina in the female, and the vasa deferentia and seminal vesicles in the male, in the second, third, fourth, and fifth lumbar nerves. The internal generative organs receive no afferent, and probably no efferent, fibres from the sacral nerves.

The position of the sympathetic ganglion-cells, the processes of which carry to their peripheral distribution the efferent impulses brought to them by the efferent vaso-motor fibres of the spinal cord, may be determined by the *nicotin method* of Langley. About 10 milligrams of nicotin injected into a vein of a cat prevent for a time, according to Langley,<sup>1</sup> any passage of nerve-impulses through a sympathetic cell. Painting the ganglion with a brush dipped in nicotin solution has a similar effect. The fibres peripheral to the cell, on the contrary, are not paralyzed by nicotin. Now, after the injection of nicotin the stimulation of the lumbar nerves in the spinal canal has no effect on the vessels of the generative organs. Hence all the vaso-motor fibres of the lumbar nerves must be connected with nerve-cells somewhere on their course. The lumbar fibres which run outward to the inferior mesenteric ganglia are for the most part connected with the cells of these ganglia. A lesser number is con-

<sup>1</sup> Langley and Anderson: *Journal of Physiology*, 1894, xvi. p. 420.



nected with small ganglia lying as a rule near the organs to which the nerves are distributed. The remaining division of lumbar fibres running downward in the sympathetic chain, and including the majority of the nerve-fibres to the external generative organs are connected with nerve-cells in the sacral ganglia of the sympathetic.

The sacral group of nerves enter ganglion-cells scattered on their course, most of the nerve-cells for any one organ being in ganglia near that organ.

*Bladder.*—Neither lumbar nor sacral nerves send vaso-motor fibres to the vessels of the bladder.

*Portal System.*—It has already been said that vaso-constrictor fibres for the portal vein were discovered by Mall in the splanchnic nerve. Constrictor fibres have been found by Bayliss and Starling<sup>1</sup> in the nerve-roots from the third to the eleventh dorsal inclusive. Most of the constrictor nerves pass out from the fifth to the ninth dorsal.

*Back.*—The dorsal branches of the lumbar and intercostal arteries, issuing from the dorsal muscles to supply the skin of the back,<sup>2</sup> can be seen to contract when the gray ramus of the corresponding sympathetic ganglia are stimulated.

*Limbs.*<sup>3</sup>—The vaso-motor nerves of the limbs in the dog leave the spinal cord from the second dorsal to the third lumbar nerves. The area for the hind limb, according to Bayliss and Bradford, is less extensive than that for the fore limb, the former receiving constrictor fibres from nine roots, namely the third to the eleventh dorsal, the latter from six roots, the eleventh dorsal to third lumbar. Langley finds that the sympathetic constrictor and dilator fibres for the fore foot are connected with nerve-cells in the ganglion stellatum; while those for the hind foot are connected with nerve-cells in the sixth and seventh lumbar, and the first, and possibly the second, sacral ganglia.

Thompson and Bancroft have studied the nerves to the superficial veins of the hind limb. The latter finds that in general the arrangement of the vaso-motor nerves corresponds to that of the arterial vaso-motor nerves and the sweat fibres. The fibres to the superficial veins originate from the lower end (first to fourth lumbar nerves) of the region of the spinal cord supplying all the vaso-motor nerves for the hind limbs.

*Tail.*<sup>4</sup>—Stimulation of any part of the sympathetic from about the third lumbar ganglion downward almost completely stops the flow of blood from wounds in the tail. The vaso-motor fibres for the tail leave the cord chiefly in the third and fourth lumbar nerves. Their stimulation may cause primary dilatation followed by constriction.

*Muscles.*—According to Gaskell, the section of the nerve belonging to

<sup>1</sup> Bayliss and Starling: *Journal of Physiology*, 1894, xvii. p. 125.

<sup>2</sup> Langley: *Journal of Physiology*, 1894, xvii. p. 314.

<sup>3</sup> Thompson: *Archiv für Physiologie*, 1893, p. 104; Wertheimer: *Archives de Physiologie*, 1894, p. 724; Bancroft: *American Journal of Physiology*, 1898, i. p. 477; Bayliss and Bradford: *Journal of Physiology*, 1894, xvi. p. 16; Langley: *Journal of Physiology*, 1894, xvii. p. 307; Piotrowski: *Archiv für die gesammte Physiologie*, 1893, lv. p. 258.

<sup>4</sup> Langley: *Journal of Physiology*, 1894, xvii. p. 311.



any particular muscle or group of muscles causes a temporary increase in the amount of blood which flows from the muscle vein. The stimulation of the peripheral end of the nerve also increases the rate of flow through the muscle. The same increase is seen on stimulation of the nerve when the muscle is kept from contracting by curare, provided the drug is not used in amounts sufficient to paralyze the vaso-dilator nerves. Mechanical stimulation by crimping the peripheral end of the nerve gives also an increase. The existence of vaso-dilator nerves to muscles must therefore be conceded. The presence of vaso-constrictor fibres is shown by the diminution in outflow from the left femoral vein which followed Gaskell's stimulation of the peripheral end of the abdominal sympathetic in a thoroughly curarized dog, but the supply of constrictor fibres is comparatively small. In curarized animals reflex dilatation apparently follows the stimulation of the nerves the excitation of which would have caused the contraction of the muscles observed, had not the occurrence of actual contraction been prevented by the curare. The stimulation of the central end of nerves not capable of calling forth reflex contractions in the muscles observed—for example, the vagus—seems to cause constriction of the muscle-vessels.

## IV. SECRETION.

### A. GENERAL CONSIDERATIONS.

THE term secretion is meant ordinarily to apply to the liquid or semi-liquid products formed by glandular organs. On careful consideration it becomes evident that the term gland itself is widely applied to a variety of structures differing greatly in their anatomical organization—so much so, in fact, that a general definition of the term covering all cases becomes very indefinite, and as a consequence the conception of what is meant by a secretion becomes correspondingly extended.

Considered from the most general standpoint we might define a gland as a structure composed of one or more gland-cells, epithelial in character, which forms a product, the secretion, that is discharged either upon a free epithelial surface such as the skin or mucous membrane, or upon the closed epithelial surface of the blood- and lymph-cavities. In the former case—that is, when the secretion appears upon a free epithelial surface communicating with the exterior, the product forms what is ordinarily known as a secretion; for the sake of contrast it might be called an external secretion. In the latter case the secretion according to modern nomenclature is designated as an internal secretion. The best-known organs furnishing internal secretions are the liver, the thyroid, and the pancreas. It remains possible, however, that any organ, even those not possessing an epithelial structure, such as the muscles, may give off substances to the blood comparable to the internal secretions—a possibility that indicates how indefinite the distinction between the processes of secretion and of general cell-metabolism may become if the analysis is carried sufficiently far. If we consider only the external secretions definition and generalization become much easier, for in these cases the secreting surface is always an epithelial structure which, when it possesses a certain organization, is designated as a gland. The type upon which these secreting surfaces are constructed is illustrated in Figure 46. The type consists of an



FIG. 46.—Plan of a secreting membrane.

epithelium placed upon a basement membrane, while upon the other side of the membrane are blood-capillaries and lymph-spaces. The secretion is derived ultimately from the blood and is discharged upon the free epithelial surface, which is supposed to communicate with the exterior. The mucous membrane of the alimentary canal from stomach to rectum may be considered,

if we neglect the existence of the villi and crypts, as representing a secreting surface constructed on this type. If we suppose such a membrane to become

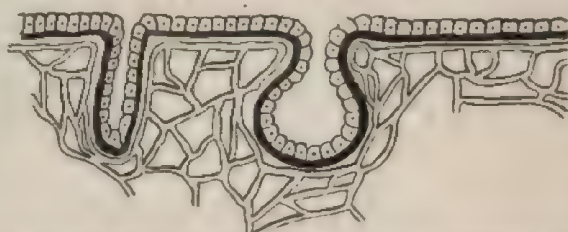


FIG. 47.—To illustrate the simplest form of a tubular and a racemose or acinous gland.

invaginated to form a tube or a sac possessing a definite lumen (see Fig. 47), we have then what may be designated technically as a gland.

It is obvious that in this case the gland may be a simple pouch, tubular or saccular in shape (Fig. 48), or it may attain a varying degree of complexity by the elongation of the involuted portion and the development of side branches



FIG. 48.—Simple alveolar gland of the amphibian skin (after Flemming).

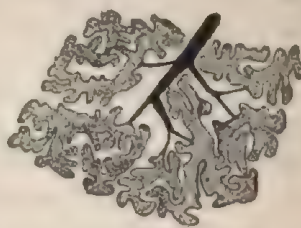


FIG. 49.—Schematic representation of a lobe of a compound tubular gland (after Flemming).

(Fig. 49). The more complex structures of this character are known sometimes as compound glands, and are further described as tubular, or racemose (saccular), or tubulo-racemose, according as the terminations of the invaginations are tubular, or saccular, or intermediate in shape.<sup>1</sup> As a matter of fact we find the greatest variety in the structure of the glands imbedded in the cutaneous and mucous surfaces, a variety extending from the simplest form of crypts or tubes to very complicated organs possessing an anatomical independence and definite vascular and nerve-supplies as in the case of the salivary glands or the kidney. In compound glands it is generally assumed that the terminal portions of the tubes alone form the secretions, and these are designated as the acini or alveoli, while the tubes connecting the alveoli with the exterior are known as the ducts, and it is supposed that their lining epithelium is devoid of secretory activity.

The secretions formed by these glands are as varied in composition as the glands are in structure. If we neglect the case of the so-called reproductive

<sup>1</sup> Flemming has called attention to the fact that most of the so-called compound racemose glands, salivary glands, pancreas, etc., do not contain terminal sacs or acini at the ends of the system of ducts; on the contrary, the final secreting portions are cylindrical tubes, and such glands are better designated as compound tubular glands.



glands, the ovary and testis, whose right to the designation of glands is doubtful, we may say that the secretions in the mammalian body are liquid or semi-liquid in character and are composed of water, inorganic salts, and various organic compounds. With regard to the last-mentioned constituent the secretions differ greatly. In some cases the organic substances present are not found in the blood, and furthermore they may be specific to a particular secretion, so that we must suppose that these constituents at least are produced in the gland itself. In other cases the organic elements may be present in the blood, and are merely eliminated from it by the gland, as in the case of the urea found in the urine. Johannes Müller long ago made this distinction, and spoke of secretions of the latter kind as excretions, a term which we still use and which carries to our minds also the implication that the substances so named are waste products whose retention would be injurious to the economy. Excretion as above defined is not a term, however, that is capable of exact application to any secretion as a whole. Urine, for example, contains some constituents that are probably formed within the kidney itself, *e. g.*, hippuric acid; while, on the other hand, in most secretions the water and inorganic salts are derived directly from the blood or lymph. So, too, some secretions—for example, the bile—carry off waste products that may be regarded as mere excretions, and at the same time contain constituents (the bile salts) that are of immediate value to the whole organism. Excretion is therefore a name that we may apply conveniently to the process of removal of waste products from the body, or to particular constituents of certain secretions, but no fundamental distinction can be made between the method of their elimination and that of the formation of secreted products in general. Owing to the diversity in composition of the various external secretions and the obvious difference in the extent to which the glandular epithelium participates in the process in different glands, a general theory of secretion cannot be formulated. The kinds of activity seem to be as varied as is the metabolism of the tissues in general.

It was formerly believed that the formation of the secretions was dependent mainly if not entirely upon the physical processes of filtration, osmosis, and diffusion. The basement membrane with its lining epithelium was supposed to constitute a membrane through which various products of the blood or lymph passed by filtration and diffusion, and the variation in composition of the secretions was referred to differences in structure and chemical properties of the dialyzing membrane. The significant point about this view is that the epithelial cells were supposed to play a passive part in the process; the metabolic processes within the cytoplasm of the cells were not believed to affect the composition of the secreted product. As compared with this view the striking peculiarity of modern ideas of secretion is, perhaps, the importance attributed to the living structure and properties of the epithelial cells. It is believed generally now that the glandular epithelium takes a direct part in the production of some at least of the constituents of the secretions. The reasons for this view will be brought out in detail further on in describing the secreting processes of the separate glands. Some of the general facts, how-

ever, which influenced physiologists in coming to this conclusion are as follows :

Microscopic examination has demonstrated clearly that in many cases parts of the epithelial cell-substance can be followed into the secretion. In the sebaceous secretion the cells seem to break down completely to form the material of the secretion ; in the formation of mucus by the goblet cells of the mucous membrane of the stomach and intestines a portion of the cytoplasm after undergoing a mucoid degeneration is extruded bodily from the cell to form the secretion ; in the mammary glands a portion of the substance of the epithelial cells is likewise broken off and disintegrated in the act of secretion, while in other glands the material of the secretion is deposited within the cell in the form of visible granules which during the act of secretion may be observed to disappear, apparently by dissolution in the stream of water passing through the cell. Facts like these show that some at least of the products of secretion arise from the substance of the gland-cells, and may be considered as representing the results of a metabolism within the cell-substance. From this standpoint, therefore, we may explain the variations in the organic constituents of the secretions by referring them to the different kinds of metabolism existing in the different gland-cells. The existence of distinct secretory nerves to many of the glands is also a fact favoring the view of an active participation of the gland-cells in the formation of the secretion. The first discovery of this class of nerve-fibres we owe to Ludwig, who (in 1851) showed that stimulation of the chorda tympani nerve causes a strong secretion from the submaxillary gland. Later investigations have demonstrated the existence of similar nerve-fibres to many other glands—for example, the lachrymal glands, the sweat-glands, the gastric glands, the pancreas. Recent microscopic work indicates that the secretory fibres end in a fine plexus between and around the epithelial cells, and we may infer from this that the action of the nerve-impulses conducted by these fibres is exerted directly upon the gland-cells.

The formation of the water and inorganic salts present in the various secretions offers a problem the general nature of which may be referred to appropriately in this connection, although detailed statements must be reserved until the several secretions are specially described. The problem involves, indeed, not only the well-recognized secretions, but also the lymph itself as well as the various normal and pathological exudations. Formerly the occurrence of these substances was explained by the action of the physical processes of filtration, diffusion, and osmosis through membranes. With the blood under a considerable pressure and with a certain concentration in salts on one side of the basement membrane, and on the other a liquid under low pressure and differing in chemical composition, it would seem inevitable that water should filter through the membrane and that processes of osmosis and diffusion should be set up, further changing the nature of the secretion. Upon this theory the water and salts in all secretions were regarded merely as transudatory products, and so far as they were concerned the epithelium was supposed to act



simply as a passive membrane. This theory has not proved entirely acceptable for various reasons. It has been shown that living membranes offer considerable resistance to filtration even when the liquid pressure on one side is much greater than on the other. 'Tigerstedt' and Santesson, for instance, found that a lung taken from a frog just killed gave no filtrate when its cavity was distended by liquid under a pressure of 18 to 20 centimeters, provided the liquid used was one that did not injure the tissue. If, however, the lung-tissue was killed by heat or otherwise, filtration occurred readily under the same pressure. In some glands, also, the formation of the water and salts, as has been said, is obviously under the control of nerve-fibres, and this fact is difficult to reconcile with the idea that the epithelial cells are merely passive filters. In glands like the kidney, and in other glands as well, it has not, as yet, been shown conclusively that the amount of water and salts increases in proportion to the rise of blood-pressure within the capillaries, as should happen if filtration were the sole agent at work; and furthermore, certain chemical substances when injected into the blood may increase the flow of urine to an extent that it is difficult to explain by the use of the filtration and diffusion theory alone.

While, therefore, it cannot be denied that the anatomical conditions prevailing in the glands are favorable to the processes of filtration and osmosis, and while we are justified in assuming that these processes do actually occur and serve to account in part for the appearance of the water and inorganic salts, it seems to be clear that in the present condition of our knowledge theories based on these factors alone do not suffice to explain all the phenomena connected with the secretion of water and salts. Until the contrary is definitively proved we may suppose that the epithelial cells are actively concerned in the process. The way in which they act is not known; various hypotheses have been advanced, but none of them meets all the facts to be explained, and at present it is customary to refer the matter to the vital properties of the cells—that is, to the peculiar physical or chemical properties connected with their living structure.

We may now pass to a consideration of the facts known with regard to the physiology of the different glands considered merely as secretory organs. The functional value of the secretions will be found described in the sections on Digestion and Nutrition.

#### **B. MUCOUS AND ALBUMINOUS (SEROUS) TYPES OF GLANDS; SALIVARY GLANDS.**

**Mucous and Albuminous Glands.**—Heidenhain recognized two types of glands, the mucous and the albuminous, basing his distinction upon the character of the secretion and upon the histological appearance of the secreting cells. The classification as originally made was applied only to the salivary glands and to similar glands found in the mucous membranes of the mouth

<sup>1</sup> *Mittheil. vom physiol. Lab. des Anat. med.-chir. Instituts in Stockholm*, 1885.



and œsophagus, the air-passages, conjunctiva, etc. The chemical difference in the secretions of the two types consists in the fact that the secretion of the albuminous (or serous) glands is thin and watery, containing in addition to possible enzymes only water, inorganic salts, and small quantities of albumin; while that of the mucous glands is stringy and viscid owing to the presence of mucin. As examples of the albuminous glands we have the parotid in man and the mammalia generally, the submaxillary in some animals (rabbit), some of the glands of the mucous membrane of the mouth and nasal cavities, and the lachrymal glands. As examples of the mucous glands, the submaxillary in man and most mammals, the sublingual, the orbital, and some of the glands of the mucous membrane of the mouth-cavity, œsophagus, and air-passages. The histological appearance of the secretory cells in the albuminous glands is in typical cases markedly different from that of the cells in the mucous glands. In the albuminous glands the cells are small and densely filled with granular material, so that the cell outlines, in preparations from the fresh gland, cannot be distinguished (see Figs. 53 and 55). In the mucous glands, on the contrary, the cells are larger and much clearer (see Fig. 56). In microscopic preparations of the fresh gland the cells, to use Langley's expression, present the appearance of ground glass, and granules are only indistinctly seen. Treatment with proper reagents brings out the granules, which are, however, larger and less densely packed than in the albuminous glands, and are imbedded in a clear homogeneous substance. Histological examination shows, moreover, that in some glands, *e. g.* the submaxillary gland, cells of both types occur. Such a gland is usually spoken of as a mucous gland, since its secretion contains mucin, but histologically it is a mixed gland. The terms mucous and albuminous or serous, as applied to the entire gland, are not in fact perfectly satisfactory, since not only do the mucous glands usually contain some secretory cells of the albuminous type, but albuminous glands, such as the parotid, may also contain cells belonging to the mucous type. The distinction is more satisfactory when it is applied to the individual cells, since the formation of mucin within a secreting cell seems to present a definite histological picture, and we can recognize microscopically a mucous cell from an albuminous cell although the two may occur together in a single alveolus.

**Goblet Cells.**—The goblet cells found in the epithelium of the intestine afford an interesting example of mucous cells. The epithelium of the intestine is a simple columnar epithelium. Scattered among the columnar cells are found cells containing mucin. These cells are originally columnar in shape like the neighboring cells, but their protoplasm undergoes a chemical change of such a character that mucin is produced, causing the cell to become swollen at its free extremity, whence the name of goblet cell. It has been shown that the mucin is formed within the substance of the protoplasm as distinct granules of a large size, and that the amount of mucin increases gradually, forcing the nucleus and a small part of the unchanged protoplasm toward the base of the

cell. Eventually the mucin is extruded bodily into the lumen of the intestine, leaving behind a partially empty cell with the nucleus and a small remnant of protoplasm (see Fig. 50). The complete life-history of these cells is imper-



FIG. 50.—Formation of secretion of mucus in the goblet cells: *A*, cell containing mucin; *B*, escape of the mucin; *C*, after escape of the mucin (after Paueth).

fectly known. According to Bizzozero<sup>1</sup> they are a distinct variety of cell and are not genetically related to the ordinary granular epithelial cells by which they are surrounded. According to others, any of the columnar epithelial cells may become a goblet cell by the formation of mucin within its interior, and after the mucin is extruded the cell regenerates its protoplasm and becomes again an ordinary epithelial cell. However this may be, the interesting fact from a physiological standpoint is that these goblet cells are genuine unicellular mucous glands. Moreover, the deposition of the mucin in the form of definite granules within the protoplasm gives histological proof that this material is produced by a metabolism of the cell-substance itself. It will be found that the mucin cells in the secreting tubules of the salivary glands exhibit similar appearances. So far as is known, the goblet cells do not possess secretory nerves.

#### SALIVARY GLANDS.

**Anatomical Relations.**—The salivary glands in man are three in number on each side—the parotid, the submaxillary, and the sublingual. The parotid gland communicates with the mouth by a large duct (Stenson's duct) which opens upon the inner surface of the cheek opposite the second molar tooth of the upper jaw. The submaxillary gland lies below the lower jaw, and its duct (Wharton's duct) opens into the mouth-cavity at the side of the frænum of the tongue. The sublingual gland lies in the floor of the mouth to the side of the frænum and opens into the mouth-cavity by a number (8 to 20) of small ducts, known as the ducts of Rivinus. One larger duct that runs parallel with the duct of Wharton and opens separately into the mouth-cavity is sometimes present in man. It is known as the duct of Bartholin and occurs normally in the dog. In addition to these three pairs of large glands a number of small glands belonging both to the albuminous and the mucous types are found imbedded in the mucous membrane of the mouth and

<sup>1</sup> *Archiv für mikroskopische Anatomie*, 1893, Bd. 42, S. 82.



tongue. The secretions of these glands contribute to the formation of the saliva.

The course of the nerve-fibres supplying the large salivary glands is interesting in view of the physiological results of their stimulation. The description here given applies especially to their arrangement in the dog. The parotid gland receives its fibres from two sources—first, cerebral fibres that originate in the glosso-pharyngeal or ninth cranial nerve, pass into a branch of this nerve known as the tympanic branch or nerve of Jacobson, thence to the small superficial petrosal nerve, through which they reach the otic ganglion. From this ganglion they pass by way of the auriculo-temporal branch of the inferior max-

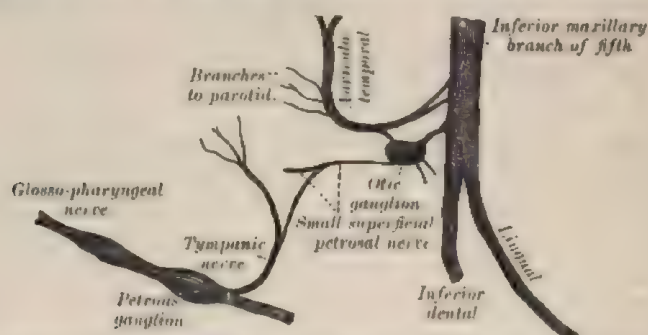


FIG. 51.—Schematic representation of the course of the cerebral fibres to the parotid gland.

illary division of the fifth cranial nerve to the parotid gland. (A schematic diagram showing the course of these fibres is given in Figure 51.) A second

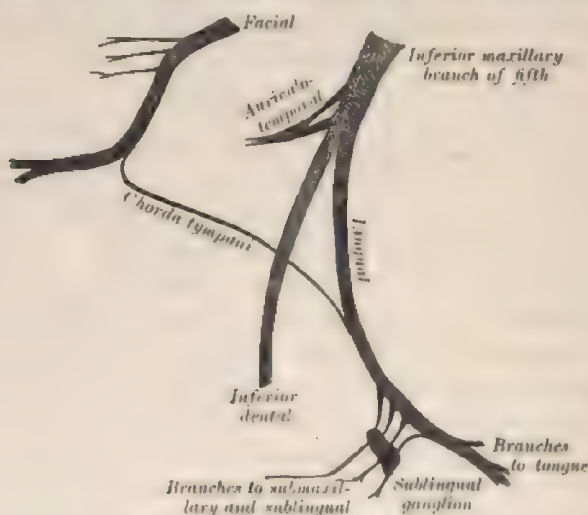


FIG. 52.—Schematic representation of the course of the chorda tympani nerve to the submaxillary gland.

supply of nerve-fibres is obtained from the cervical sympathetic nerve, the fibres reaching the gland ultimately in the coats of the blood-vessels. The submaxillary (and the sublingual) glands receive their nerve-fibres also from

two sources. The cerebral fibres arise from the brain in the facial nerve and pass out in the chorda tympani branch (Fig. 52). This latter nerve, after emerging from the tympanic cavity through the Glaserian fissure, joins the lingual nerve. After running with this nerve for a short distance, the secretory (and vaso-dilator) nerve-fibres destined for the submaxillary and sublingual glands branch off and pass to the glands, following the course of the ducts. Where the chorda tympani fibres leave the lingual there is a small ganglion which has received the name of submaxillary ganglion. The nerve-fibres to the glands pass close to this ganglion, but Langley has shown that only those destined for the sublingual gland really connect with the nerve-cells of the ganglion, and he suggests therefore that it should be called the sublingual instead of the submaxillary ganglion. The nerve-fibres for the submaxillary gland make connections with nerve-cells mainly within the hilus of the gland itself. The submaxillary and sublingual glands receive also sympathetic nerve-fibres, which after leaving the superior cervical ganglion pass to the glands in the coats of the blood-vessels.

**Histological Structure.**—The salivary glands belong to the type of compound tubular glands, as Flemming has pointed out. That is, the secreting portions are tubular in shape, although in cross sections these tubes may present various outlines according as the plane of the section passes through them. The parotid is described usually as a typical serous or albuminous gland. Its secreting epithelium is composed of cells which in the fresh condition as well as in preserved specimens contain numerous fine granules (see Figs. 53 and 55, A). Heidenhain states that in exceptional cases (in the dog) some of the secreting cells may belong to the mucous type. The basement membrane is composed of flattened branched connective-tissue cells, the interstices between which are filled by a thin membrane. The submaxillary gland differs in histology in different animals. In some, as the dog or cat, all the secretory tubes are composed chiefly or exclusively of epithelial cells of the mucous type (Fig. 56). In man the gland is of a mixed type, the secretory tubes containing both mucous and albuminous cells. The sublingual gland in man also contains both varieties of cells, although the mucous cells predominate. It follows from these histological characteristics that the secretion from the submaxillary and sublingual glands is thick and mucilaginous as compared with that from the parotid.

In the mucous glands another variety of cells, the so-called demilunes or crescent cells, is frequently met with; and the physiological significance of these cells has been the subject of much discussion. The demilunes are crescent-shaped granular cells lying between the mucous cells and the basement membrane, and not in contact, therefore, with the central lumen of the tube (see Fig. 56). According to Heidenhain these demilunes are for the purpose of replacing the mucous cells. In consequence of long-continued activity the mucous cells may disintegrate and disappear, and the demilunes then develop into new mucous cells. The most probable view at present is that the demilunes represent distinct secretory cells of the albuminous type.



The secreting tubules of the salivary glands possess distinct lumens round which the cells are arranged. In addition a number of recent observers, making use of the Golgi method of staining, have apparently demonstrated that in the albuminous glands the lumen is continued as fine capillary spaces running between the secreting cells.<sup>1</sup> The statement is also made that from these secretion capillaries small side-branches are given off that penetrate into the substance of the cell, making an intracellular origin of the system of ducts; this point, however, needs confirmation. In the mucous glands similar secretion capillaries are found only in connection with the demilunes. This latter fact supports the view that the demilunes are not simply inactive forms of mucous cells, but cells with a specific functional activity. It is an undoubted fact that the salivary glands possess definite secretory nerves which when stimulated start the formation of secretion. This fact indicates that there must be a direct contact of some kind between the gland-cells and the terminations of the secretory fibres. The nature of this connection has been the subject of numerous investigations, the results of which were for a long time negative or untrustworthy. More recently, however, the application of the useful Golgi method has led to satisfactory results. The ending of the nerve-fibres in the submaxillary and sublingual glands has been described by a number of observers.<sup>2</sup> The accounts differ somewhat as to details of the finer anatomy, but it seems to be clearly established that the secretory fibres from the chorda tympani end first round the intrinsic nerve-ganglion cells of the glands, and from these latter cells axis-cylinders are distributed to the secreting cells, passing to these cells along the ducts. The nerve-fibres terminate in a plexus upon the membrana propria of the alveoli, and from this plexus fine fibrils pass inward to end on and between the secreting cells. It would seem from these observations that the nerve-fibrils do not penetrate or fuse with the gland-cells, as was formerly supposed, but form a terminal network in contact with the cells, following thus the general schema for the connection between nerve-fibres and peripheral tissues.

**Composition of the Secretion.**—The saliva as it is found in the mouth is a mixed secretion from the large salivary glands and the numerous smaller glands scattered over the mucous membrane of the mouth. It is a colorless or opalescent, turbid, and mucilaginous liquid of weakly alkaline reaction and a specific gravity of about 1003. It may contain numerous flat cells derived from the epithelium of the mouth, and the peculiar spherical cells known as salivary corpuscles, which seem to be altered leucocytes. The important constituents of the secretion are mucin, a diastatic enzyme known as ptyalin, traces of albumin and of potassium sulphocyanide, and inorganic salts such as potassium and sodium chloride, potassium sulphate, sodium carbonate, and calcium carbonate and phosphate. The average proportions of these constituents is given in the following analysis by Hammerbacher:

<sup>1</sup> Lasestein: *Pflüger's Archiv für die gesammte Physiologie*, 1893, Bd. 55, S. 417.

<sup>2</sup> See Huber: *Journal of Experimental Medicine*, 1896, vol. i. p. 281.

Water, . . . . .	994.203
Solids:	
Mucin and epithelial cells, . . . . .	2.202
Ptyalin and albumin, . . . . .	1.300
Inorganic salts, . . . . .	2.205
	<hr/> 5.797
	1.000.000

(Potassium sulphocyanide, 0.041.)

Of the organic constituents of the saliva the proteid exists in small and variable quantities, and its exact nature is not determined. The mucin gives to the saliva its ropy, mucilaginous character. This substance belongs to the group of combined proteids, glyco-proteids (see section on Chemistry), consisting of a proteid combined with a carbohydrate group. The physiological value of this constituent seems to lie in its physical properties, as described in the section on Digestion. The most interesting constituent of the mixed saliva is the ptyalin. This body belongs to the group of enzymes or unorganized ferments, whose general and specific properties are described in the section on Digestion. It suffices here to say only that ptyalin belongs to the diastatic group of enzymes, whose specific action consists in a conversion of the starches into sugar by a process of hydrolysis. In some animals (dog) ptyalin seems to be normally absent from the fresh saliva. An interesting fact with reference to the saliva is the large quantity of gases, particularly  $\text{CO}_2$ , which may be obtained from it when freshly secreted. In an analysis by Pflüger of the saliva from the submaxillary gland the following figures were obtained:  $\text{CO}_2$ , 65 per cent., of which 42.5 per cent. was in the form of carbonates; N, 0.8 per cent.; O, 0.6 per cent. For the parotid secretion Kälz reports:  $\text{CO}_2$ , 66.7 per cent., of which 62 per cent. was in combination as carbonate; N, 3.8 per cent.; O, 1.46 per cent.

The secretions of the parotid and submaxillary glands can be obtained easily by inserting a cannula into the openings of the ducts in the mouth. The secretion of the sublingual can only be obtained in sufficient quantities for analysis from the lower animals. Examination of the separate secretions shows that the main difference lies in the fact that the parotid saliva contains no mucin, while that of the submaxillary and especially of the sublingual gland is rich in mucin. The parotid saliva of man seems to be particularly rich in ptyalin as compared with that of the submaxillary, while the secretion of the latter and that of the sublingual gland give a stronger alkaline reaction than the parotid saliva.

**The Secretory Nerves.**—The existence of secretory nerves was discovered by Ludwig in 1851. He found that stimulation of the chorda tympani nerve caused a flow of saliva from the submaxillary gland. He established also several important facts with regard to the pressure and composition of the secretion which will be referred to presently. It was afterward shown that the salivary glands receive a double nerve-supply, in part by way of the cervical sympathetic and in part through cerebral nerves, as briefly described on p. 218. It was discovered also that not only are secretory fibres carried



to the glands by these paths, but that the vaso-motor fibres are contained in the same nerves, and the arrangement of these latter fibres is such that the cerebral nerves contain vaso-dilator fibres that cause a dilatation of the small arteries in the glands and an accelerated blood-flow, while the sympathetic carries vaso-constrictor fibres whose stimulation causes a constriction of the small arteries and a diminished blood-flow. The effect upon the secretion of stimulating these two sets of fibres is found to vary somewhat in different animals. For purposes of description we may confine ourselves to the effects observed on dogs, since much of our fundamental knowledge upon the subject is derived from Heidenhain's<sup>1</sup> experiments upon this animal. If the chorda tympani nerve is stimulated by weak induction shocks, the gland begins to secrete promptly, and the secretion, by proper regulation of the stimuli, may be kept up for hours. The secretion thus obtained is thin and watery, flows freely, is abundant in amount, and contains not more than 1 or 2 per cent. of total solids. At the same time there is an increased flow of blood through the gland. The whole gland takes on a redder hue, the veins are distended, and if cut the blood that flows from them is of a redder color than in the resting gland, and may show a distinct pulse—all of which points to a dilatation of the small arteries. If now the sympathetic fibres are stimulated, quite different results are obtained. The secretion is relatively small in amount, flows slowly, is thick and turbid, and may contain as much as 6 per cent. of total solids. At the same time the gland becomes pale, and if the veins be cut the flow from them is slower than in the resting gland, thus indicating that a vaso-constriction has occurred.

The increased vascular supply to the gland accompanying the abundant flow of "chorda saliva" and the diminished flow of blood during the scanty secretion of "sympathetic saliva" suggest naturally the idea that the whole process of secretion may be at bottom a vaso-motor phenomenon, the amount of secretion depending only on the quantity and pressure of the blood flowing through the gland. It has been shown conclusively that this idea is erroneous and that definite secretory fibres exist. The following facts may be quoted in support of this statement: (1) Ludwig showed that if a mercury manometer is connected with the duct of the submaxillary gland and the chorda is then stimulated for a certain time, the pressure in the duct may become greater than the blood-pressure in the gland. This fact shows that the secretion is not derived entirely by processes of filtration from the blood. (2) If the blood-flow be shut off completely from the gland, stimulation of the chorda will still give a secretion for a short time. (3) If atropin is injected into the gland, stimulation of the chorda will cause vascular dilatation but no secretion. This may be explained by supposing that the atropin paralyzes the secretory but not the dilator fibres. (4) Hydrochlorate of quinine injected into the gland gives vascular dilatation but no secretion. In

<sup>1</sup> *Pflüger's Archiv für die gesammte Physiologie*, 1878, Bd. xvii. S. 1; also in *Hermann's Handbuch der Physiologie*, 1883, Bd. v. Th. 1.

this case the secretory fibres are still irritable, since stimulation of the chorda gives the usual secretion.

A still more marked difference between the effect of stimulation of the cerebral and the sympathetic fibres may be observed in the case of the parotid gland in the dog. Stimulation of the cerebral fibres alone in any part of their course (see Fig. 51) gives an abundant thin and watery saliva, poor in solid constituents. Stimulation of the sympathetic fibres alone (provided the cerebral fibres have not been stimulated shortly before (Langley) and the tympanic nerve has been cut to prevent a reflex effect) gives usually no perceptible secretion at all. But in this last stimulation a marked effect is produced upon the gland, in spite of the absence of a visible secretion; this is shown by the fact that subsequent or simultaneous stimulation of the cerebral fibres gives a secretion very unlike that given by the cerebral fibres alone, in that it is very rich indeed in organic constituents. The amount of organic matter in the secretion may be tenfold that of the saliva obtained by stimulation of the cerebral fibres alone.

Another important and suggestive set of facts with regard to the action of the secretory nerves is obtained from a study of the differences in composition of the secretion following upon variations in the strength of stimulation of the nerves.

*Relation of the Composition of the Secretion to the Strength of Stimulation.*—If the stimulus to the chorda is gradually increased in strength, care being taken not to fatigue the gland, the chemical composition of the secretion is found to change with regard to the relative amounts of the water, the salts, and the organic material. The water and the salts increase in amount with the increased strength of stimulus up to a certain maximal limit, which for the salts is about 0.77 per cent. It is important to observe that this effect may be obtained from a perfectly fresh gland as well as from a gland which had previously been secreting actively. With regard to the organic constituents the precise result obtained depends on the condition of the gland. If previous to the stimulation the gland was in a resting condition and unfatigued, then increased strength of stimulation is followed at first by a rise in the percentage of organic constituents, and this rise in the beginning is more marked than in the case of the salts. But with continued stimulation the increase in organic material soon ceases, and finally the amount begins actually to diminish, and may fall to a low point in spite of the stronger stimulation. On the other hand, if the gland in the beginning of the experiment had been previously worked to a considerable extent, then an increase in the stimulating current, while it increases the amount of water and salts, may have either no effect at all upon the organic constituents or cause only a temporary increase, quickly followed by a fall. Similar results may be obtained from stimulation of the cerebral nerves of the parotid gland. The above facts led Heidenhain to believe that the conditions determining the secretion of the organic material are different from



those controlling the water and salts, and he gave a rational explanation of the differences observed, in his theory of trophic and secretory fibres.

**Theory of Trophic and Secretory Nerve-fibres.**—This theory supposes that two physiological varieties of nerve-fibres are distributed to the salivary glands. One of these varieties controls the secretion of the water and inorganic salts and its fibres may be called secretory fibres proper, while the other, to which the name trophic is given, causes the formation of the organic constituents of the secretion, probably by a direct influence on the metabolism in the cell. Were the trophic fibres to act alone, the organic products would be formed within the cell but there would be no visible secretion, and this is the hypothesis which Heidenhain uses to explain the results of the experiment described above upon stimulation of the sympathetic fibres to the parotid of the dog. In this animal, apparently, the sympathetic branches to the parotid contain exclusively or almost exclusively trophic fibres, while in the cerebral branches both trophic and secretory fibres proper are present. The results of stimulation of the cerebral and sympathetic branches to the submaxillary gland of the same animal may be explained in terms of this theory by supposing that in the latter nerve trophic fibres preponderate, and in the former the secretory fibres proper.

It is obvious that this anatomical separation of the two sets of fibres along the cerebral and sympathetic paths may be open to individual variations, and that dogs may be found in which the sympathetic branches to the parotid glands contain secretory fibres proper, and therefore give some flow of secretion on stimulation. These variations might also be expected to be more marked when animals of different groups are compared. Thus Langley<sup>1</sup> finds that in cats the sympathetic saliva from the submaxillary gland is less viscid than the chorda saliva, just the reverse of what occurs in the dog. To apply Heidenhain's theory to this case it is necessary to assume that in the cat the trophic fibres run chiefly in the chorda. An interesting fact with reference to the secretion of the parotid in dogs has been noted by Langley and is of special interest, since, although it may be reconciled with the theory of trophic and secretory fibres, it is at the same time suggestive of an incompleteness in this theory. As has been said, stimulation of the sympathetic in the dog causes usually no secretion from the parotid. Langley<sup>2</sup> finds, however, that if the tympanic nerve is stimulated just previously, stimulation of the sympathetic causes an abundant but brief flow from the parotid. One may explain this in terms of the theory by assuming that the sympathetic does contain a few secretory fibres proper, but that ordinarily their action is too feeble to start the flow of water. Previous stimulation of the tympanic nerve, however, leaves the gland-cells in a more irritable condition, so that the few secretory fibres proper in the sympathetic branches are now effective in producing a flow of water.

<sup>1</sup> *Journal of Physiology*, 1878, vol. i. p. 96.

<sup>2</sup> *Ibid.*, 1889, vol. x. p. 291.

**Theories of the Action of Trophic and Secretory Fibres.**—The way in which the trophic fibres act has been briefly indicated. They may be supposed to set up metabolic changes in the protoplasm of the cells, leading to the formation of certain definite products, such as mucin or ptyalin. That such changes do occur is abundantly shown by microscopic examination of the resting and the active gland, the details of which will be given presently. In general these changes may be supposed to be katabolic in nature; that is, to consist in a disassociation or breaking down of the complex living material with the formation of the simpler and more stable organic constituents of the secretion. There is evidence to show that these gland-cells during activity form fresh material from the nourishment supplied by the blood; that is, that anabolic or building-up processes occur along with the katabolic changes. The latter are the more obvious and are the changes which are usually associated with the action of the trophic nerve-fibres. It is possible, also, that the anabolic or growth changes may be under the control of separate fibres for which the name anabolic fibres would be appropriate. Satisfactory proof of the existence of a separate set of anabolic fibres has not yet been furnished.

The method of action of the secretory fibres proper is difficult to understand. At present the theories suggested are very speculative, and a detailed account of them is scarcely appropriate in this place. Heidenhain's own view may be mentioned, but it should be borne in mind that it is only an hypothesis, the truth of which is far from being demonstrated. The theory starts from the fact that no more water leaves the blood-capillaries than afterward appears in the secretion; that is, no matter how long the secretion continues, the gland does not become cedematous nor does the velocity of the lymph-stream in the lymphatics of the gland increase. This being the case, we must suppose that the stream of water is regulated by the secretion, that is, by the activity of the gland-cells. If we suppose that some constituent of these cells has an attraction for water, or, to use the modern expression, exerts a high osmotic pressure, then, while the gland is in the resting state, water will diffuse from the basement membrane; this in turn supplies its loss from the surrounding lymph, and the lymph obtains the same amount of water from the blood. As the amount of water in the cell increases a point is reached at which an equilibrium is established, and the osmotic stream from blood to cells comes to a standstill. The water in the cells does not escape into the lumen of the tubule or of the secretion capillaries, because the periphery of the cell is modified to form a layer offering considerable resistance to filtration. The action of the secretory fibres proper consists in so altering the structure of this limiting layer of the cells that it offers less resistance to filtration; consequently the water under tension in the cells escapes into the lumen, and the osmotic pressure of its substance again starts up a stream of water from capillaries to cells, which continues as long as the nerve-stimulation is effective.



Recent work by Ranvier, Drasch, Biedermann, and others has called attention to an interesting phenomenon occurring in gland-cells during secretion which when better known will possibly throw light upon the formation of the water stream under the influence of nerve-stimulation. Ranvier<sup>1</sup> describes in both serous and mucous cells the formation of vacuoles within the protoplasmic substance. These vacuoles are particularly abundant after nerve-stimulation. They seem to contain water, and if they behave as they do in the protozoa—and this is indicated by the observations of Drasch<sup>2</sup> upon the glands in the nictitating membrane in the frog—they would seem to form a mechanism sufficient to force water from the cells into the lumen.

**Histological Changes during Activity.**—The cells of both the albuminous and mucous glands undergo distinct histological changes in consequence of prolonged activity, and these changes may be recognized both in preparations from the fresh gland and in preserved specimens. In the parotid gland Heidenhain studied the changes in stained sections after hardening in alcohol. In the resting gland (Fig. 53) the cells are compactly filled with

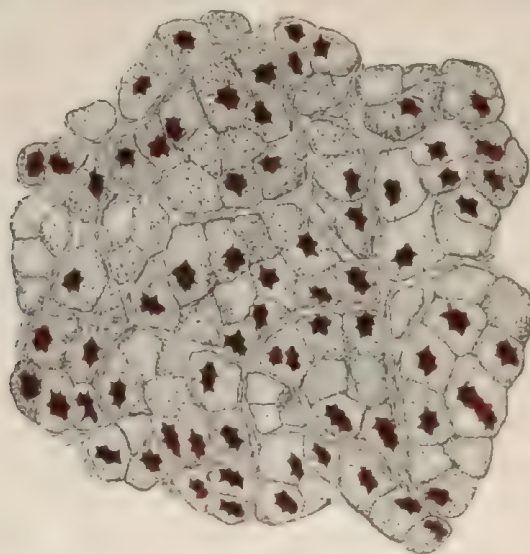


FIG. 53.—Parotid of the rabbit, in the resting condition (after Heidenhain).

granules that stain readily and are imbedded in a clear ground substance that does not stain. The nucleus is small and more or less irregular in outline. After stimulation of the tympanic nerve the cells show but little alteration, but stimulation of the sympathetic produces a marked change (Fig. 54). The cells become smaller, the nuclei more rounded, and the granules more closely packed. This last appearance seems, however, to be due to the hardening reagents used. A truer picture of what occurs may be obtained from a study of sections of the fresh gland. Langley,<sup>3</sup> who first used this method,

<sup>1</sup> *Comptes rendus*, cxviii, 4, p. 168.    <sup>2</sup> *Archiv für Anatomie und Physiologie*, 1889, S. 96.

<sup>3</sup> *Journal of Physiology*, 1879, vol. ii. p. 260.

describes his results as follows: When the animal is in a fasting condition the cells have a granular appearance throughout their substance, the outlines of

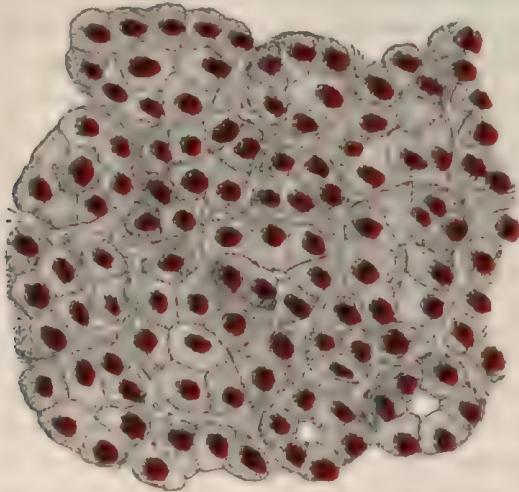


FIG. 54.—Parotid of the rabbit, after stimulation of the sympathetic (after Heidenhain).

the different cells being faintly marked by light lines (Fig. 55, *A*). When the gland is made to secrete by giving the animal food, by injecting pilocarpin, or by stimulating the sympathetic nerves, the granules begin to disappear from



FIG. 55.—Parotid gland of the rabbit in a fresh state, showing portions of the secreting tubules: *A*, in a resting condition; *B*, after secretion caused by pilocarpin; *C*, after stronger secretion, pilocarpin and stimulation of sympathetic; *D*, after long-continued stimulation of sympathetic (after Langley).

the outer borders of the cells (Fig. 55, *B*), so that each cell now shows an outer clear border and an inner granular one. If the stimulation is continued the granules become fewer in number and are collected near the lumen and the mar-



gins of the cells, the clear zone increases in extent and the cells become smaller (Fig. 55, *C, D*). Evidently the granular material is used up in some way to make the organic material of the secretion. Since the ptyalin is a conspicuous organic constituent of the secretion, it is assumed that the granules in the resting gland contain the ptyalin, or rather a preliminary material from which the ptyalin is constructed during the act of secretion. On this latter assumption the granules are frequently spoken of as zymogen granules. During the act of secretion two distinct processes seem to be going on in the cell, leaving out of consideration for the moment the formation of the water and the salts. In the first place the zymogen granules undergo a change such that they are forced or dissolved out of the cell, and, second, a constructive metabolism or anabolism is set up, leading to the formation of new protoplasmic material from the substances contained in the blood and lymph. The new material thus formed is the clear, non-granular substance, which appears first toward the basal sides of the cells. We may suppose that the clear substance during the resting periods undergoes metabolic changes, whether of a katabolic or anabolic character cannot be safely asserted, leading to the formation of new granules, and the cells are again ready to form a secretion of normal composition. It should be borne in mind that in these experiments the glands were stimulated beyond normal limits. Under ordinary conditions the cells are probably never depleted of their granular material to the extent represented in the figures.

In the cells of the mucous glands changes equally marked may be observed after prolonged activity. In stained sections of the resting gland, according to Heidenhain, the cells are large and clear (Fig. 56), with flattened nuclei



FIG. 56.—Mucous gland: submaxillary of dog: resting stage.

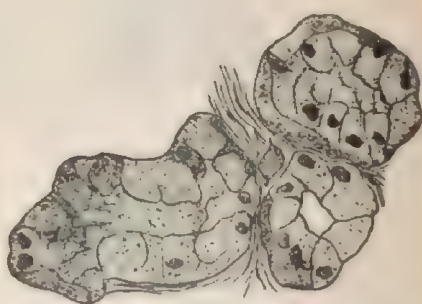


FIG. 57.—Mucous gland: submaxillary of dog after eight hours' stimulation of the chorda tympani.

placed well toward the base of the cell. When the gland is made to secrete the nuclei become more spherical and lie more toward the middle of the cell, and the cells themselves become distinctly smaller. After prolonged secretion the changes become more marked (Fig. 57) and, according to Heidenhain, some of the mucous cells may break down completely. According to most of the later observers, however, the mucous cells do not actually disintegrate, but

form again new material during the period of rest as was described for the goblet cells of the intestine. In the mucous as in the albuminous cells observations upon pieces of the fresh gland seem to give more reliable results than those upon preserved specimens. Langley<sup>1</sup> has shown that in the fresh mucous cells of the submaxillary gland numerous large granules may be discovered, about 125 to 250 to a cell. These granules are comparable to those found in the goblet cells, and may be interpreted as consisting of mucin or some preparatory material from which mucin is formed. The granules are sensitive to reagents; addition of water causes them to swell up and disappear. It may be assumed that this happens during secretion, the granules becoming converted to a mucin-mass which is extruded from the cell.

**Action of Atropin, Pilocarpin, and Nicotin upon the Secretory Nerves.**—The action of drugs upon the salivary glands and their secretions belongs properly to pharmacology, but the effects of the three drugs mentioned are so decided that they have a peculiar physiological interest. Atropin in small doses injected either into the blood or into the gland-duct prevents the action of the cerebral fibres (tympanic nerve or chorda tympani) upon the glands. This effect may be explained by assuming that the atropin paralyzes the endings of the cerebral fibres in the glands. That it does not act directly upon the gland-cells themselves seems to be assured by the interesting fact that with doses sufficient to throw out entirely the secreting action of the cerebral fibres, the sympathetic fibres are still effective when stimulated. Pilocarpin has directly the opposite effect to atropin. In minimal doses it sets up a continuous secretion of saliva, which may be explained upon the supposition that it stimulates the endings of the secretory fibres in the gland. Within certain limits these drugs antagonize each other—that is, the effect of pilocarpin may be removed by the subsequent application of atropin and *vice versa*. Nicotin, according to the experiments of Langley,<sup>2</sup> prevents the action of the secretory nerves, not by action on the gland-cells or the endings of the nerve-fibres round them, but by paralyzing the connections between the nerve-fibres and the ganglion cells through which the fibres pass on their way to the gland. If, for example, the superior cervical ganglion is painted with a solution of nicotin, stimulation of the cervical sympathetic below the gland will give no secretion; stimulation, however, of the fibres in the ganglion or between the ganglion and gland will give the usual effect. By the use of this drug Langley is led to believe that the cells of the so-called submaxillary ganglion are really intercalated in the course of the fibres to the sublingual gland, while the nerve-cells with which the submaxillary fibres make connection are found chiefly in the hilus of the gland itself.

**Paralytic Secretion.**—A remarkable phenomenon in connection with the salivary glands is the so-called paralytic secretion. It has been known for a long time that if the chorda tympani is cut the submaxillary gland after a certain time, one to three days, begins to secrete slowly and the secretion contin-

<sup>1</sup> *Journal of Physiology*, 1889, vol. x. p. 433.

<sup>2</sup> *Proceedings of the Royal Society*, London, 1889, vol. xli. p. 423.



ues uninterruptedly for a long period—as long, perhaps, as several weeks—and eventually the gland itself undergoes atrophy. Langley<sup>1</sup> states that section of the chorda on one side is followed by a continuous secretion from the glands on both sides; the secretion from the gland of the opposite side he designates as the antiparalytic or antilytic secretion. After section of the chorda the nerve-fibres peripheral to the section degenerate, the process being completed within a few days. These fibres, however, do not run directly to the gland-cell; they terminate in end-arborizations round sympathetic nerve-cells placed somewhere along their course, in the sub-lingual ganglion, for instance, or within the gland substance itself. It is the axons from these second nerve units that end round the secreting cells. Langley<sup>2</sup> has accumulated some facts to show that within the period of continuance of the paralytic secretion (5 to 6 weeks) the fibres of the sympathetic cells are still irritable to stimulation. He is inclined to believe therefore that the continuous secretion is due to a continuous excitation, from some cause, of the local nervous mechanism in the gland. On the other hand, it is possible that the mere cessation of the normal action of the chorda fibres is followed by an altered metabolism in the gland cells of such a nature as to cause a continuous feeble secretion.

**Normal Mechanism of Salivary Secretion.**—Under normal conditions the flow of saliva from the salivary glands is the result of a reflex stimulation of the secretory nerves. The sensory fibres concerned in this reflex must be chiefly fibres of the glosso-pharyngeal and lingual nerves supplying the mouth and tongue. Sapid bodies and various other chemical or mechanical stimuli applied to the tongue or mucous membrane of the mouth will produce a flow of saliva. The normal flow during mastication must be effected by a reflex of this kind, the sensory impulse being carried to a centre and thence transmitted through the efferent nerves to the glands. It is found that section of the chorda prevents the reflex, in spite of the fact that the sympathetic fibres are still intact. No satisfactory explanation of the normal functions of the secretory fibres in the sympathetic has yet been given. Various authors have suggested that possibly the three large salivary glands respond normally to different stimuli. This view has lately been supported by Pawlow, who reports that in the dog at least the parotid and the submaxillary may react quite differently. When fistulas were made of the ducts of these glands it was found that the submaxillary responded readily to a great number of stimuli, such as the sight of food, chewing of meats, acids, etc. The parotid, on the contrary, seemed to react only when dry food, dry powdered meat, or bread was placed in the mouth. Dryness in this case seemed to be the efficient stimulus. Since the flow of saliva is normally a definite reflex, we should expect a distinct salivary secretion centre. This centre has been located by physiological means in the medulla oblongata; its exact position is not clearly defined, but possibly it is represented by the nuclei of origin of

<sup>1</sup> *Proceedings of the Royal Society*, London, 1885, No. 236.

<sup>2</sup> *Text-book of Physiology*, edited by Schäfer, 1898.

the secretory fibres which leave the medulla by way of the facial and glosso-pharyngeal nerves. Owing to the wide connections of nerve-cells in the central nervous system we should expect this centre to be affected by stimuli from various sources. As a matter of fact, it is known that the centre and through it the glands may be called into activity by stimulation of the sensory fibres of the sciatic, splanchnic, and particularly the vagus nerves. So, too, various psychical acts, such as the thought of savory food and the feeling of nausea preceding vomiting, may be accompanied by a flow of saliva, the effect in this case being due probably to stimulation of the secretion centre by nervous impulses descending from the higher nerve-centres. Lastly, the medullary centre may be inhibited as well as stimulated. The well-known effect of fear, embarrassment, or anxiety in producing a parched throat may be supposed to arise in this way by the inhibitory action of nerve-impulses arising in the cerebral centres.

**Electrical Changes in the Gland during Activity.**—It has been shown that the salivary as well as other glands suffer certain changes in electric potential during activity which are comparable in a general way to the "action currents" observed in muscles and nerves (see section on Muscle and Nerve). The theories bearing upon the causes of these electrical changes are too intricate and speculative to enter upon here. The reader is referred to an account given by Biedermann<sup>1</sup> for further details.

### C. PANCREAS; GLANDS OF THE STOMACH AND INTESTINES.

**Anatomical Relations of the Pancreas.**—The pancreas in man lies in the abdominal cavity behind the stomach. It is a long, narrow gland, its head lying against the curvature of the duodenum and its narrow extremity or tail reaching to the spleen. The chief duct of the gland (duct of Wirsung) usually opens into the duodenum, together with the common bile-duct, about eight to ten centimeters below the pylorus. In some cases, at least, a smaller duct may enter the duodenum separately somewhat lower down. The points at which the ducts of the pancreas open into the duodenum vary considerably in different animals. For instance, in the dog there are two ducts, the larger of which enters the duodenum separately about six to seven centimeters below the pylorus, while in the rabbit the main duct opens into the duodenum over thirty centimeters below the pylorus. The nerves of the pancreas are derived from the solar plexus, but physiological experiments which will be described presently show that the gland receives fibres from at least two sources, through the vagus nerve and through the sympathetic system.

**Histological Characters.**—The pancreas, like the salivary glands, belongs to the compound tubular type. The cells in the secreting portions of the tubules, the so-called alveoli, belong to the serous or albuminous type, and are usually characterized by the fact that the outer portion of each cell, that is, the part toward the basement membrane, is composed of a clear non-glandular

<sup>1</sup> *Elektrophysiologie*, Jena, 1895.



substance that takes stains readily, while the inner portion turned toward the lumen is filled with conspicuous granules. In addition to this type of cell, which is the characteristic secreting element of the organ, the pancreas contains a number of irregular masses of cells of a different character (bodies of Langerhans). These latter cells are clear and small, frequently have ill-defined cell-bodies, but contain nuclei which stain readily with ordinary reagents. By some these cells are supposed to be immature secreting cells of the ordinary pancreatic type. By others it is thought that they are a separate type of cell and take some special part in the secretory functions of the pancreas. Nothing definite, however, is known as to their physiological importance.

**Composition of the Pancreatic Secretion.**—The pancreatic secretion is a clear alkaline liquid which in some animals (dog) is thick and mucilaginous. Its physical characters seem to vary greatly, even in the same animal, according to the duration of the secretion or the time since the establishment of the fistula by which it is obtained (see p. 300). In a newly made fistula in the dog the secretion is thick, but in a permanent fistula it becomes much thinner and more watery. The main constituents of the secretion are three enzymes, a large percentage of proteid material the exact nature of which is not known, some fats, soaps, a slight amount of lecithin, and inorganic salts. The strongly alkaline nature seems to be due chiefly to sodium carbonate, which may be present in amounts equal to 0.2 to 0.4 per cent. The three enzymes are known respectively as trypsin, a proteolytic ferment; amyllopsin, a diastatic ferment, and steapsin, a fat-splitting ferment. The action of these enzymes in digestion is described in the section on Digestion.

**Action of the Nerves on the Secretion of the Pancreas.**—In animals like the dog, in which the process of digestion is not continuous, the secretion of the pancreas is also supposed to be intermittent. A study of the flow of secretion as observed in cases of pancreatic fistula indicates that it is connected with the beginning of digestion in the stomach, and is therefore probably a reflex act. Until recently, however, little direct evidence had been obtained of the existence of secretory nerves. Stimulation of the medulla was known to increase the flow of pancreatic juice and to alter its composition as regards the organic constituents, but direct stimulation of the vagus and the sympathetic nerves gave only negative results. Lately, however, Pawlow<sup>1</sup> and some of his students have been able to overcome the technical difficulties in the way, and have given what seems to be perfectly satisfactory proof of the existence of distinct secretory fibres comparable in their nature to those described for the salivary glands. The results that they have obtained may be stated briefly as follows: Stimulation of either the vagus nerve or the sympathetic causes, after a considerable latent period, a marked flow of pancreatic secretion. The failure of other experimenters to get this result was due apparently to the sensitiveness of the gland to variations in its blood-supply. Either direct or reflex

<sup>1</sup> Pawlow: *Du Bois-Reymond's Archiv für Physiologie*, 1893, Suppl. Bd.; Mett: *Ibid.*, 1894; Kudrewetsky: *Ibid.*, 1894; Pawlow: *Die Arbeit der Verdauungsdrüsen*, Wiesbaden, 1898.

vaso-constriction of the pancreas prevents the action of the secretory nerves upon it. Thus stimulation of the sympathetic gives usually no effect upon the secretion, because vaso-constrictor fibres are stimulated at the same time, but if the sympathetic nerve is cut five or six days previously, so as to give the vaso-constrictor fibres time to degenerate, stimulation will cause, after a long latent period, a distinct secretion of the pancreatic juice. A similar result may be obtained from stimulating the undegenerated nerve if mechanical stimulation is substituted for the electrical.

The long latent period elapsing between the time of stimulation and the effect upon the flow is not easily understood. The authors quoted do not give an entirely satisfactory explanation of this curious fact, but suggest that it may be due to the presence of definite inhibitory fibres to the gland, which are stimulated simultaneously with the secretory fibres and thus hold the secretion in check for a time. The existence of inhibitory fibres is rendered probable by several interesting experiments, for an account of which the original sources must be consulted.<sup>1</sup>

**Histological Changes during Activity.**—The morphological changes in the pancreatic cells have long been known and have been studied satisfactorily in the fresh gland as well as in preserved specimens. The general nature of the changes is the same as that described for the salivary gland, and is illustrated in Figures 58, 59, and 60. If the gland is removed from a dog which has been fasting for about twenty-four hours and is hardened in alcohol and sectioned and stained, it will be found that the cells are filled with granules except for a narrow zone toward the basal end, which is marked off more clearly because it stains more deeply than the granular portion (Fig. 58). If, on the contrary, the gland is taken from a dog which had been fed

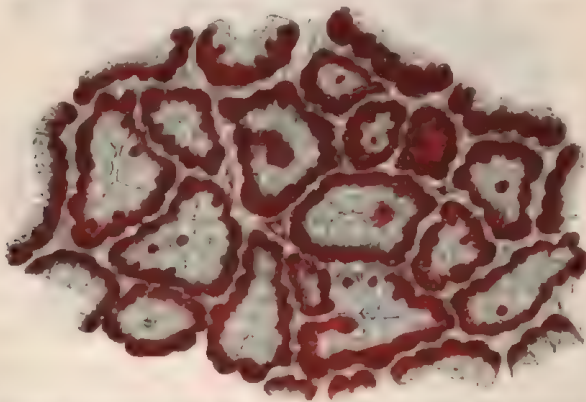


FIG. 58.—Pancreas of the dog during hunger, preserved in alcohol and stained in carmine (after Heidenhain)

six to ten hours previously, the non-staining granular zone is much reduced in size, while the clearer non-granular zone is enlarged (Fig. 59). The increase in size of the non-granular zone does not, however, entirely compensate for

<sup>1</sup> Pawlow: *Die Arbeit der Verdauungsdrüsen*, p. 78, Wiesbaden, 1898.



the loss of the granular material, so that the cell as a whole is smaller in size than in the gland from the fasting animal. It seems evident that during the hours immediately following a meal—that is, at the time when we know

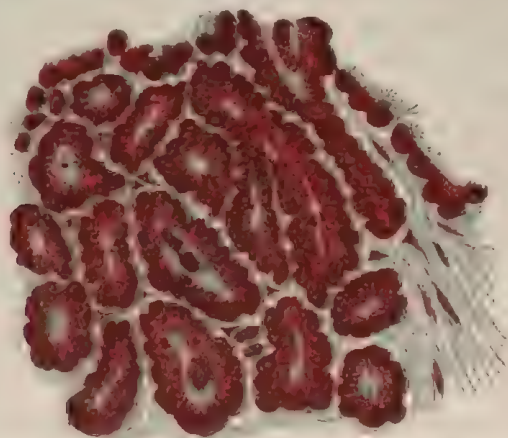


FIG. 59.—Pancreas of dog during first stage of digestion; alcohol, carmine (after Heidenhain).

that the gland is discharging its secretion, the granular material is being used up. After the cessation of active secretion—that is, during the tenth to the twentieth hour after a meal in the case of a dog fed once in twenty-four

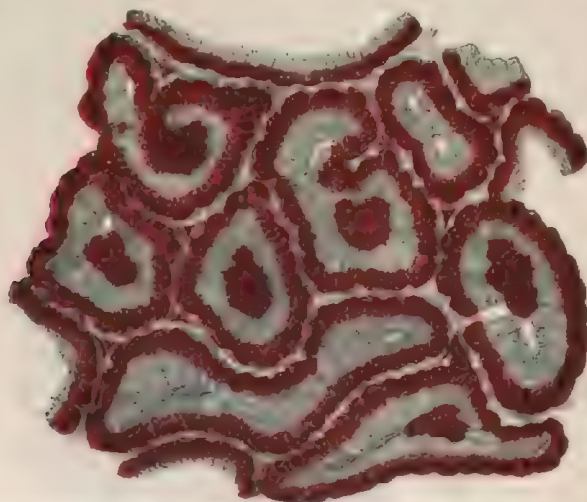


FIG. 60.—Pancreas of dog during second stage of digestion; alcohol, carmine (after Heidenhain).

hours—the gland-cells return to their resting condition (Fig. 60). New granules are formed, and finally, if the gland is left unstimulated they fill the entire cell except for a narrow margin at the basal end.

Similar results are reported by Kühne<sup>1</sup> and Lea from observations made upon the pancreas cells in a living rabbit. In the inactive gland the outlines

<sup>1</sup> *Untersuchungen aus dem physiologischen Institut der Universität Heidelberg*, 1882, Bd. ii.

of the individual cells are not clearly distinguishable, but it can be seen that there are two zones, one clear and homogeneous on the side toward the basement membrane, and one granular on the side toward the lumen. During activity the secretory tubules show a notched appearance corresponding to the positions of the cells, the outlines of the cells become more distinct, the granular zone becomes smaller, and the homogeneous zone increases in width. It should be stated also that in this latter condition the basal zone of the cells shows a distinct striation. From these appearances we must believe that, as in the case of the salivary gland, a part at least of the organic material of the secretion is formed from the granules of the inner zone, and that the granules in turn are formed within the cells from the homogeneous material of the outer zone.

*Enzyme and Zymogen.*—The observations just described indicate that the enzymes of the pancreatic secretion are derived from the granules in the cells, but other facts show that the granules do not contain the enzymes as such, but a preparatory material or mother-substance to which the name zymogen (enzyme-maker) is given. This belief rests upon facts of the following kind: If a pancreas is removed from a dog that has fasted for twenty-four hours, when, as we have seen, the cells are heavily loaded with granules, and a glycerin extract is made, very little active enzyme will be found in it. If, however, the gland is allowed to stand for twenty-four hours in a warm spot before the extract is made, or if it is first treated with dilute acetic acid, the glycerin extract will show very active tryptic or amylolytic properties. Moreover, if an inactive glycerin extract of the perfectly fresh gland is treated by various methods, such as dilution with water or shaking with finely divided platinum-black, it becomes converted to an active extract capable of digesting proteid material. These results are readily explained upon the hypothesis that the granules contain only zymogen material, which during the act of secretion, or by means of the methods mentioned, may be converted into the corresponding enzymes. As the three enzymes of the pancreatic secretion seem to be distinct substances, one may suppose that each has its own zymogen to which a distinctive name might be given. The zymogen that is converted into trypsin is frequently spoken of as trypsinogen.

*Normal Mechanism of Pancreatic Secretion.*—After the establishment of a pancreatic fistula it is possible to study the flow of secretion in its relations to the ingestion of food. Experiments of this kind have been made. They show that in animals like the dog, in which sufficient food may be taken in a single meal to last for a day, the flow of secretion is intimately connected with the reception of food into the stomach and its subsequent digestive changes. The time relations of the secretion to the ingestion of food are shown in the accompanying chart (Fig. 61). The secretion begins immediately after the food enters the stomach, and increases in velocity up to a certain maximum which is reached some time between the first and the third hour after the meal. The velocity then diminishes rapidly to the fifth or sixth hour, after which there may be a second smaller increase reaching its maximum about the ninth to the eleventh hour. From this point the secretion



diminishes in quantity to the sixteenth or seventeenth hour, when it has practically reached the zero point. In man, in whom the meals normally occur at intervals of five to six hours, this curve of course would have a different form. The interesting fact, however, that the secretion starts very soon

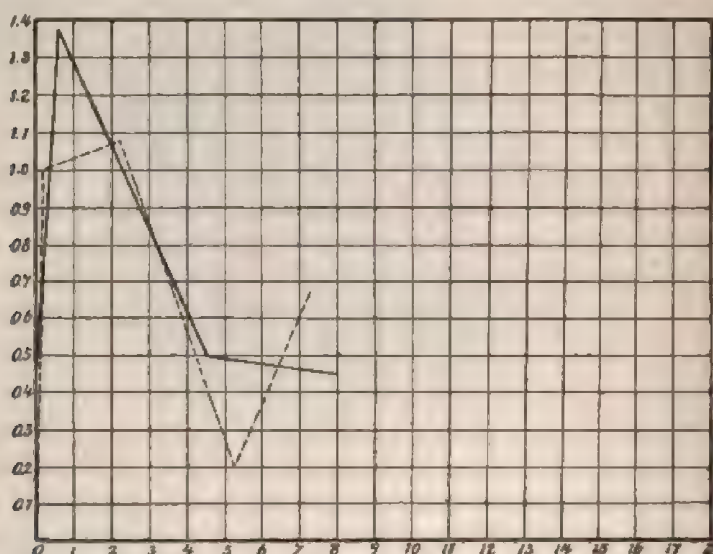


FIG. 61.—Curve of the secretion of pancreatic juice during digestion. The figures along the abscissa represent hours after the beginning of digestion: the figures along the ordinate represent the quantity of this secretion in cubic centimeters. Curves of two experiments are given (after Heidenhain).

after the beginning of gastric digestion is probably true for human beings, and gives strong indication that the secretion is a reflex act.

Recently a number of experiments have been reported which strengthen the view that the normal secretion of the pancreas is reflexly excited by stimuli acting upon the mucous membrane of the stomach or duodenum. Dolinsky,<sup>1</sup> working upon dogs by Pawlow's methods, finds that acids are particularly effective in arousing the pancreatic flow; on the contrary, alkalies in the stomach diminish the pancreatic secretion. Dolinsky believes that the normal acidity of the gastric secretion is perhaps the most effective stimulus to the pancreatic gland, and that in this way the flow of gastric juice in ordinary digestion starts the pancreatic gland into activity. Whether the acid acts after absorption into the blood, or stimulates the sensory fibres of the mucous membrane, and thus reflexly affects the pancreas through its secretory nerves, is not definitely known, but the probabilities are in favor of the latter view. It is probable also that the acid acts upon the sensory fibres of the mucous membrane of the duodenum rather than upon the gastric membrane.

In addition to acids, it has been found that oils and water introduced into the stomach also cause a flow of pancreatic juice, the stimulation occurring prob-

<sup>1</sup> *Archives des Sciences biologiques*, St. Petersburg, 1895, t. iii. p. 399.

ably after these substances have reached the duodenum. Moreover, Pawlow has given proof that the secretion of the pancreas varies in both quantity and quality with the nature of the food. Indeed, there seem to be indications of a specific relationship between the food and the composition of the secretion, albuminous food giving a secretion with a greater digestive action on proteids; oily foods, a secretion with a larger amount of fat-splitting enzymes, and so on. If this relationship is shown to exist, it forms an adaptation whose mechanism is very obscure.<sup>1</sup>

#### GLANDS OF THE STOMACH.

**Histological Characteristics.**—The glands of the gastric mucous membrane belong practically to the type of simple tubular glands; for, although two or more of the simple tubes may possess a common opening or mouth, there is no system of ducts such as prevails in the compound glands, and the divergence from the simplest form of tubular gland is very slight. Each of these glands possesses a relatively wide mouth, lined with the columnar epithelium found on the free surface of the gastric membrane, and a longer, narrower secreting part, which penetrates the thickness of the mucosa and is lined by cuboidal cells. The glands in the pyloric end of the stomach differ in general appearance from those in the fundic end, and are especially characterized by the fact that they possess only one kind of secretory cell, while the fundic glands contain two apparently distinct types of cells (Fig. 64). The lumen in the latter glands is lined by a continuous layer of short cylindrical cells to which Heidenhain gave the name of chief-cells. These cells are apparently concerned in the formation of pepsin, the proteolytic enzyme contained in the gastric secretion. In addition there are present a number of cells of an oval or triangular shape which are placed close to the basement membrane and do not extend quite to the main lumen of the gland. These cells are not found in the pyloric glands; they are known by various names, such as border-cells, parietal cells, oxyntic cells, etc. The last-mentioned name has been given to them because of their supposed connection with the formation of the acid of the gastric secretion. The nature and function of these border-cells have been the subject of much discussion. From the histological side they have been interpreted as representing either immature forms of the chief-cell, or else the active modification of this cell. Recent work, however, seems to have demonstrated that they form a specific type of cell, and probably therefore have a specific function. An interesting histological fact in connection with the parietal cells is that, in the human stomach at least, they frequently contain several nuclei, five or six, and some of these seem to be derived from ingested leucocytes. They are interesting also is the fact that they contain distinct vacuoles that seem to appear some time after digestion has begun, reach a maximum size, and then gradually grow smaller and finally disappear. Like the similar phenomenon

<sup>1</sup> For other interesting facts bearing upon the mechanism of pancreatic secretion, see Walter: *Archives des Sciences biologiques*, 1899, t. vii. p. 1.



described for other gland-cells (p. 226), this appearance is possibly connected with the formation of the secretion.

The duct of a gastric gland was formerly supposed to be a simple tube extending the length of the gland. A number of recent observers, however,

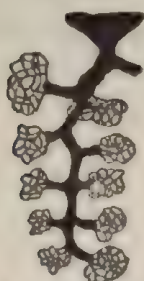


FIG. 62.—Ducts and secretion capillaries to parietal cells. Gland from the fundus of cat's stomach (after Langendorff and Laserstein).

have shown, by the use of the Golgi stain, that this view is not entirely correct, at least not for the glands in the fundus in which border-cells are present. In these glands the central lumen sends off side channels that pass to the border-cells and there form a network of small capillaries lying either in or round the cell.<sup>1</sup> An illustration of the duct-system of a fundic gland is given in Figure 62. If this work is correct it would seem that the chief-cells communicate directly with the central lumen, but that the border-cells have a system of secretion capillaries of their own, resembling in this respect the demilunes of the mucous salivary glands (p. 220). This

fact tends to corroborate the statement previously made, that the border-cells form a distinct type of cell whose function is probably different from that of the chief-cells.

#### Composition of the Secretion of the Gastric Mucous Membrane.—

The secretion as it is poured out on the surface of the mucous membrane is composed of the true secretion of the gastric glands together with more or less mucus, which is added by the columnar cells lining the surface of the membrane and the mouths of the glands. In addition to the mucus, water, and inorganic salts, the secretion contains as its characteristic constituents hydrochloric acid and two enzymes—namely, pepsin which acts upon proteids, and rennin which has a specific coagulating effect upon the casein of milk. For an analysis of the gastric secretion of the dog see p. 288. According to Heidenhain,<sup>2</sup> the secretion from the pyloric end of the stomach is characterized by the absence of hydrochloric acid, although it still contains pepsin. This statement rests upon careful experiments in which the pyloric end was entirely resected and made into a blind pouch which was then sutured to the abdominal wall to form a fistula. In this way the secretion of the pyloric end could be obtained free from mixture with the secretion of any other part of the alimentary canal. By this means Heidenhain found that the pyloric secretion is an alkaline liquid containing pepsin. This fact forms the strongest evidence for Heidenhain's hypothesis that the HCl of the normal gastric secretion is produced by the "border-cells" of the fundic glands and the pepsin by the "chief-cells," since HCl is formed only in parts of the stomach containing border-cells, whereas the pepsin is produced in the pyloric end, where only chief-cells are present.

Evidence of this character is naturally not very convincing, and the hypoth-

<sup>1</sup> Langendorff and Laserstein: *Pflüger's Archiv für die gesammte Physiologie*, 1894, Bd. lv. S. 578.

<sup>2</sup> *Archiv für die gesammte Physiologie*, 1878, Bd. xviii. S. 169, also Bd. xix.

esis, especially that part connecting the border-cells with the formation of HCl, can only be accepted provisionally until further investigation confirms or disproves it. It should be stated that the alkalinity of the secretion obtained from the pyloric glands by Heidenhain's method has been attributed by some authors to the abnormal conditions prevailing, especially to the section of the vagus fibres that necessarily results from the operation. Contejean<sup>1</sup> asserts that the reaction of the pyloric membrane under normal conditions is acid in spite of the absence of border-cells.

**Influence of the Nerves upon the Gastric Secretion.**—It has been very difficult to obtain direct evidence of the existence of extrinsic secretory nerves to the gastric glands. In the hands of most experimenters, stimulation of the vagi and of the sympathetics has given negative results, and, on the other hand, section of these nerves does not seem to prevent entirely the formation of the gastric secretion. There are on record, however, a number of observations that point to a direct influence of the central nervous system on the secretion. Thus Bidder and Schmidt found that in a hungry dog with a gastric fistula (page 288) the mere sight of food caused a flow of gastric juice; and Richet reports a case of a man in whom the œsophagus was completely occluded and in whom a gastric fistula was established by surgical operation. It was then found that savory foods chewed in the mouth produced a marked flow of gastric juice. There would seem to be no clear way of explaining the secretions in these cases except upon the supposition that they were caused by a reflex stimulation of the gastric mucous membrane through the central nervous system. These cases are strongly supported by some recent experimental work on dogs by Pawlow<sup>2</sup> and Schunowa-Simanowskaja. These observers used dogs in which a gastric fistula had been established, and in which, moreover, the œsophagus had been divided in the neck and the upper and lower cut surfaces brought to the skin and sutured so as to make two fistulous openings. In these animals, therefore, food taken into the mouth and subsequently swallowed escaped to the exterior through the upper œsophageal fistula, without entering the stomach. Nevertheless this "fictitious meal," as the authors designate it, brought about a secretion of gastric juice. If in such animals the two vagi were cut, the "fictitious meal" no longer caused a secretion of the gastric juice, and this fact may be considered as showing that the secretion obtained when the vagi were intact was due to a reflex stimulation of the stomach through these nerves. In later experiments<sup>3</sup> from the same laboratory the secretion caused in this way by the act of eating is designated as a "psychical secretion," on the assumption, for which considerable evidence is given, that the reflex must involve psychical factors such as the sensations accompanying the provocation and gratification of the appetite. In favorable cases the fictitious feeding was continued for as long as five to six hours, with the production of a secretion of about 700 c.c. of pure gastric

<sup>1</sup> *Archives de Physiologie*, 1892, p. 554.

<sup>2</sup> *Du Bois-Reymond's Archiv für Physiologie*, 1895, 8, 53.

<sup>3</sup> *Die Arbeit der Verdauungsdrüsen*, Wiesbaden, 1898.



juice. Finally, these observers were able to show that direct stimulation of the vagi under proper conditions causes, after a long latent period (four and a half to ten minutes), a marked secretion of gastric juice. The long latent period is attributed to the simultaneous stimulation of inhibitory fibres.

Taking these results together, we must believe that the vagi send secretory fibres to the gastric glands, and that these fibres may be stimulated reflexly through the sensory nerves of the mouth, and probably also by psychical states.

**Normal Mechanism of Secretion of the Gastric Juice.**—Our knowledge of the means by which the flow of gastric secretion is caused during normal digestion, and of the varying conditions which influence the flow, is as yet quite incomplete. The notable experiments recently made by Pawlow<sup>1</sup> and his pupils, together with older experiments by Heidenhain,<sup>2</sup> have, however, thrown some light upon this difficult problem, and have, moreover, opened the way for further experimental study of the matter. Heidenhain cut out a part of the fundus of the stomach, converted it into a blind sac, and brought one end of the sac to the abdominal wall so as to form a fistulous opening to the exterior. The continuity of the stomach was established by suturing the cut ends, but the fundic sac was completely separated from the rest of the alimentary canal. This operation has since been modified by Pawlow in such a way that the isolated fundic sac retains its normal nerve supply. Heidenhain found that under these conditions the ingestion of ordinary food caused a secretion in the isolated and empty fundic sac, the secretion beginning fifteen to thirty minutes after the food was taken, and continuing until the stomach was empty. The ingestion of water caused a temporary secretion in the fundus, while indigestible material such as ligamentum nuchæ gave no secretion at all. Heidenhain's interpretation of these experiments as applied to normal secretion was that in ordinary digestion we must distinguish between a primary and a secondary secretion. The primary secretion depends upon the mechanical stimulus of the ingested food, and is confined to the spots directly stimulated; the secondary secretion begins after absorption from the stomach is in progress, and involves the whole secreting surface. The first part of this theory is in accord with a belief which heretofore has been very generally held by physiologists, namely, that the gastric glands may be made to secrete by direct mechanical excitation. Pawlow has shown, however, by what seem to be most convincing experiments, that this belief is erroneous. Mechanical stimulation, strong or weak, circumscribed or general, seems to be totally without effect in arousing a secretion. Pawlow has been led by his interesting experiments to give a different explanation of the normal mechanism of secretion. The first effect of eating is the production of the "psychical secretion," before referred to. This secretion is effected through the action of secretory fibres in the vagus, and possibly also in the sympathetic nerve. It begins usually within five minutes, is, in a general way, proportional in amount

<sup>1</sup> *Archives des Sciences biologiques*, St. Petersburg, 1895, t. iii. p. 461; t. v. p. 425.

<sup>2</sup> *Hermann's Handbuch der Physiologie*, 1883, Bd. v. S. 114.

to the intensity of the appetite or enjoyment of the food, and may last for several hours even though the actual period of eating has been short (five minutes). It is this secretion that first acts upon the food received into the stomach. Later its action is supplemented by an augmented secretion, caused by stimuli of a chemical nature originating in the food ingested. Some foods contain substances ready formed that are capable of acting in this way. Investigation of various articles of diet showed that meat extracts, juices, and soups contain these substances in largest amounts. Milk and aqueous solutions of gelatin act in the same way, although less powerfully. Water also, if in sufficient quantity, acts as a direct stimulant. Other common articles of food, such as bread or white of egg, do not contain these stimulating substances. Food of the latter character, when introduced directly into a dog's stomach through a fistula, provokes not a drop of secretion and undergoes no digestion, if it has been introduced in such a way as to avoid arousing the psychical secretion, as, for instance, at times when the animal is dozing. If, however, this latter class of foods undergo digestion, as would happen in normal feeding in consequence of the action of the "psychical secretion," substances capable of stimulating the stomach to secretion are developed, and their action keeps up the flow of secretion after the effect of the psychical factor has become weakened. The nature of these chemical

stimuli remains entirely undetermined. Pawlow's first statement that pepsin constituted at least one member of this group he now finds is erroneous. It is assumed that these substances act through the secretory nerves, and it has been shown also that other substances may have the contrary effect of retarding or inhibiting the gastric secretion. This has been proved for fats at least. Oils of various kinds decrease the secretion of gastric juice, while they augment the pancreatic secretion. Another most suggestive result of Pawlow's work is the proof that the quantity and characteristics of the secretion vary with the food. Apparently the quantity of the secretion varies, other

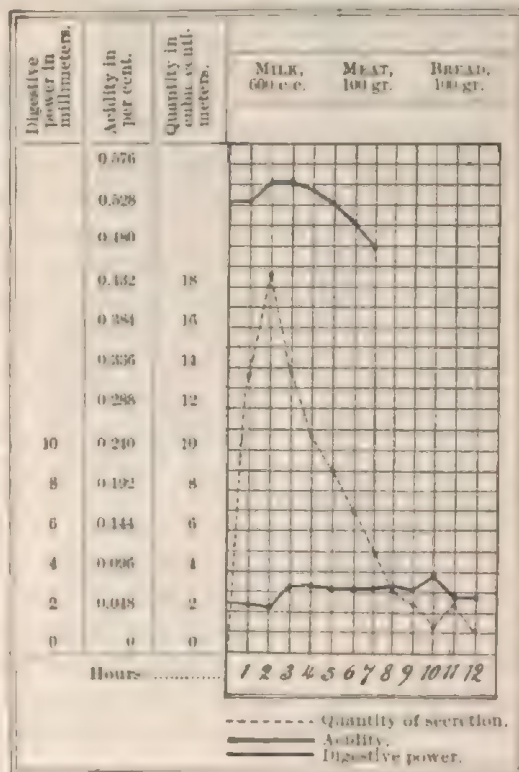


FIG. 63.—Diagram showing the variation in quantity of gastric secretion in the dog after a mixed meal; also the variations in acidity and in digestive power after Khigine).



conditions being the same, with the amount of the food to be digested. By some means the apparatus is adjusted in this respect to work economically. Different kinds of food produce secretions varying not only as regards quantity, but also in their acidity and digestive action. The secretion produced by bread, though less in quantity than that caused by meat, possesses a greater digestive action. On a given diet the secretion will assume certain characteristics, and Pawlow is convinced that further work will disclose the fact that the secretion of the stomach is not caused normally by general stimuli all affecting it alike, but by specific stimuli contained in the food or produced during digestion, whose action is of such a kind as to produce the secretion best adapted for the food ingested.

One of the curves showing the effect of a mixed diet (milk, 600 cubic centimeters; meat, 100 grams; bread, 100 grams) upon the gastric secretion, as determined by Pawlow's method, is reproduced in Fig. 63. It will be noticed that the secretion began shortly after the ingestion of the food (seven minutes), and increased rapidly to a maximum that was reached in two hours. After the second hour the flow decreased rapidly and nearly uniformly to about the tenth hour. The acidity rose slightly between the first and second hours, and then fell gradually. The digestive power showed an increase between the second and third hours.

**Histological Changes in the Gastric Glands during Secretion.**—The cells of the gastric glands, especially the so-called chief-cells, show distinct changes as the result of prolonged activity. Upon preserved specimens taken from dogs fed at intervals of twenty-four hours, Heidenhain found that in the fasting condition the chief-cells were large and clear, that during the first six hours of digestion the chief-cells as well as the border-cells increased in size, but that in a second period extending from the sixth to the fifteenth hour, the chief-cells became gradually smaller, while the border-cells remained large or even increased in size. After the fifteenth hour the chief-cells increased in size, gradually passing back to the fasting condition (see Fig. 64).

Langley<sup>1</sup> has succeeded in following the changes in a more satisfactory way by observations made directly upon the living gland. He finds that the chief-cells in the fasting stage are charged with granules, and that during digestion the granules are used up, disappearing first from the base of the cell, which then becomes filled with a non-granular material. Observations similar to those made upon the pancreas demonstrate that these granules represent in all probability a preliminary material from which the gastric enzymes are made during the act of secretion. The granules, therefore, as in the other glands, may be spoken of as zymogen granules, the preliminary material of the pepsin being known as pepsinogen and that of the rennin sometimes as pexinogen.

**Glands of the Intestine.**—At the very beginning of the intestine in the immediate neighborhood of the pylorus is found a small area of mucous membrane containing distinct tubular glands, known usually as the glands of

<sup>1</sup> *Journal of Physiology*, 1880, vol. iii. p. 269.

Brunner. These glands resemble closely in arrangement those of the pyloric end of the stomach, with the exception that the tubular duct is more branched. The secreting cells are similar to those of the pyloric glands of the stomach. Little is known of their secretion. According to some authors it contains pepsin. The amount of secretion furnished by these glands would seem to be too small to be of great importance in digestion. Throughout the length

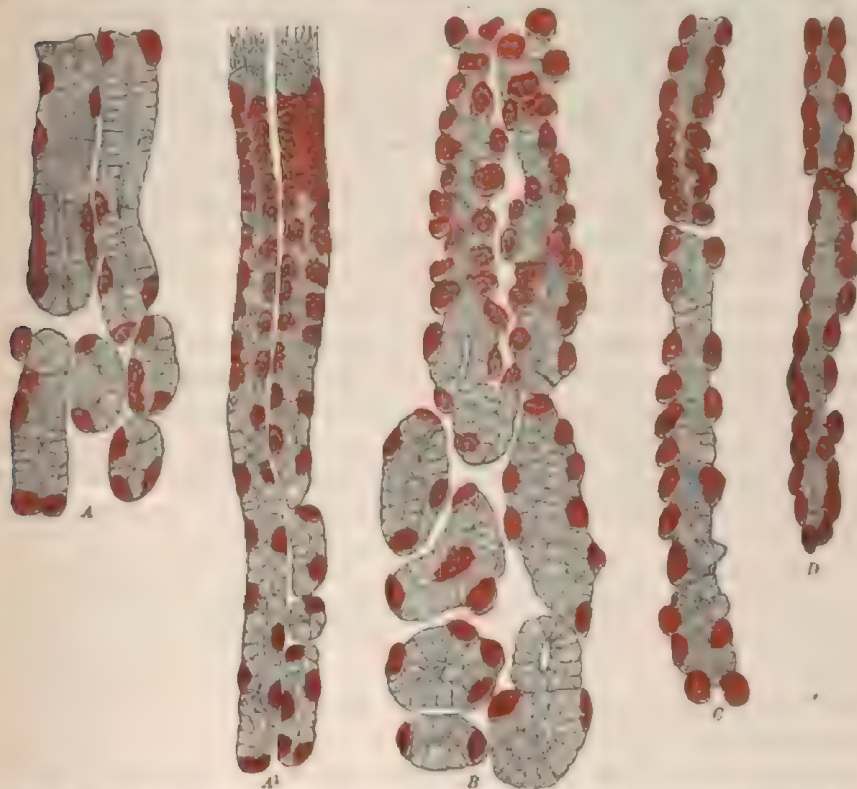


FIG. 64.—Glands of the fundus (dog): *A* and *A'*, during hunger, resting condition; *B*, during the first stage of digestion; *C* and *D*, the second stage of digestion, showing the diminution in the size of the "chief" or central cells (after Heidenhain).

of the small and large intestine the well-known crypts of Lieberkühn are found. These structures resemble the gastric glands in general appearance, but not in the character of the epithelium. The epithelium lining the crypts is of two varieties—the goblet cells, whose function is to form mucus, and columnar cells with a characteristic striated border. The changes in the goblet cells during secretion and the probability of a relationship between them and the neighboring epithelial cells has been discussed (see p. 216). Whether or not the crypts form a definite secretion has been much debated. Physiologists are accustomed to speak of an intestinal juice, "*succus entericus*," as being formed by the glands of Lieberkühn, but practically nothing is known as to the mechanism of the secretion. The *succus entericus* itself, however it may be formed, can be collected by isolating small loops of the intestine and



bringing the ends to the abdominal wall to form fistulous openings. The secretion thus obtained contains diastatic and also inverting ferments, the action of which is described on p. 308. Histologically, the cells in the bottom of the crypts do not possess the general characteristics of secreting cells.

#### D. LIVER; KIDNEY.

The liver is a gland belonging to the compound tubular type. The hepatic cells represent the secretory cells and the bile-ducts carry off the external secretion, which is designated as bile. In addition it is known that the liver-cells occasion important changes in the material brought to them in the blood, and that two important compounds, namely, glycogen and urea, are formed under the influence of these cells and afterward are given off to the blood-stream. The liver, then, furnishes a conspicuous example of a gland that forms simultaneously an external and an internal secretion. In this section we have to consider only certain facts in relation to the external secretion, the bile.

**Histological Structure.**—The general histological relations of the hepatic lobules need not be repeated in detail. It will be remembered that in each lobule the hepatic cells are arranged in columns radiating from the central vein, and that the intralobular capillaries are so arranged with reference to these columns that each cell is practically brought into contact with a mixed blood derived in part from the portal vein and in part from the hepatic artery.

As a gland making an external secretion, the relations of the liver-cells to the ducts and to the nervous system are important points to be determined. The bile-ducts can be traced without difficulty to the fine interlobular branches running round the periphery of the lobules, but the finer branches or bile-capillaries springing from the interlobular ducts and penetrating into the interior of the lobules have been difficult to follow with exactness, especially as to their connection with the interlobular ducts on the one hand, and with the liver-cells on the other. The bile-capillaries have long been known to penetrate the columns of cells in the lobule in such a way that each cell is in contact with a bile-capillary at one point of its periphery, and with a blood-capillary at another, the bile- and blood-capillaries being separated from each other by a portion of the cell-substance. But whether or not intracellular branches from these capillaries actually penetrate into the substance of the liver-cells has been a matter in dispute. Kuppfer contended that delicate ducts arising from the capillaries enter into the cells and end in a small intracellular vesicle. As this appearance was obtained by forcible injections through the bile-ducts, it was thought by many to be an artificial product; but recent observations with staining reagents tend to substantiate the accuracy of Kuppfer's observations and confirm the belief that normally the system of bile-ducts begins within the liver-cells in minute channels that connect directly with the bile-capillaries.

Two questions with reference to the bile-ducts have given rise to considerable

discussion and investigation : first, the relationship existing between the liver-cells and the lining epithelium of the bile-ducts ; second, the presence or absence of a distinct membranous wall for the bile-capillaries. Different opinions are still held upon these points, but the balance of evidence seems to show that the bile-capillaries have no proper wall. They are simply minute tubular spaces penetrating between the liver-cells and corresponding to the alveolar lumen in other glands. Where the capillaries join the interlobular ducts the liver-cells pass gradually or abruptly, according to the class of vertebrates examined, into the lining epithelium of the ducts. From this standpoint, then, the liver-cells are homologous to the secreting cells of other glands in their relations to the general lining epithelium. Several observers (MaCallum,<sup>1</sup> Berkley,<sup>2</sup> and Korolkow<sup>3</sup>) have claimed that they are able to trace nerve-fibres to the liver-cells, thus furnishing histological evidence that the complex processes occurring in these cells are under the regulating control of the central nervous system. According to the latest observers (Berkeley, Korolkow) the terminal nerve-fibrils end between the liver-cells, but do not actually penetrate the substance of the cells, as was described in some earlier papers. If these observations prove to be entirely correct they would demonstrate the direct effect of the nervous system on some at least of the manifold activities of the liver-cells. So far as the formation of the bile is concerned we have no satisfactory physiological evidence that it is under the control of the nervous system.

**Composition of the Secretion.**—The bile is a colored secretion. In most carnivorous animals it is golden red, while in the herbivora it is green, the difference depending on the character and quantity of the pigments. In man the bile is usually stated to follow the carnivorous type, showing a reddish or brownish color, although in some cases apparently the green predominates. The characteristic constituents of the bile are the pigments, *bilirubin* in carnivorous bile and *biliverdin* in herbivorous bile, and the bile acids or bile-salts, the sodium salts of glycocholic or taurocholic acid, the relative proportions of the two acids varying in different animals. In addition there is present a considerable quantity of a mucoid nucleo-albumin, a constituent which is not formed in the liver-cells, but is added to the secretion by the mucous membrane of the bile-ducts and gall-bladder ; and small quantities of cholesterin, lecithin, fats, and soaps. The inorganic constituents comprise the usual salts—chlorides, phosphates, carbonates and sulphates of the alkalis or alkaline earths. Iron is found in small quantities, combined probably as a phosphate. The secretion contains also a considerable though variable quantity of CO<sub>2</sub> gas, held in such loose combination that it can be extracted with the gas-pump, without the addition of acid. The presence of this constituent serves as an indication of the extensive metabolic changes occurring in the liver-cells. Quantitative analyses of the bile show that it varies greatly in composition even in the same species of animal. Examples of this variability are given in the analyses

<sup>1</sup> MaCallum : *Quarterly Journal of the Microscopical Sciences*, 1887, vol. xxvii. p. 439.

<sup>2</sup> Berkley : *Anatomischer Anzeiger*, 1893, Bd. viii. S. 769.      <sup>3</sup> Korolkow : *Ibid.*, S. 750.



quoted in the section on Digestion (p. 322), where a brief account will also be found of the origin and physiological significance of the different constituents.

**The Quantity of Bile Secreted.**—Owing to the fact that a fistula of the common bile-duct or gall-bladder may be established upon the living animal and the entire quantity of bile be drained to the exterior without serious detriment to the animal's life, we possess numerous statistics as to the daily quantity of the secretion formed. Surgical operations upon human beings (see p. 321 for references), made necessary by occlusion of the bile-passages, have furnished similar data for man. In round numbers the quantity in man varies from 500 to 800 cubic centimeters per day, or, taking into account the weight of the individuals concerned, about 8 to 16 cubic centimeters for each kilogram of body-weight. Observations upon the lower animals indicate that the secretion is proportionally greater in smaller animals. This fact is clearly shown in the following table, compiled by Heidenhain<sup>1</sup> for three herbivorous animals:

	Sheep	Rabbit.	Guinea-pig.
Ratio of bile-weight for 24 hours to body-weight . . .	1:37.5	1:8.2	1:5.6
Ratio of bile-weight for 24 hours to liver-weight . . .	1.507:1	4.064:1	4.467:1

There seems to be no doubt that the bile is a continuous secretion, although in animals possessing a gall-bladder the secretion may be stored in this reservoir and ejected into the duodenum only at certain intervals connected with the processes of digestion. The movement of the bile-stream within the system of bile-ducts—that is, its actual ejection from the liver, is also probably intermittent. The observations of Copeman and Winston on a human patient with a biliary fistula showed that the secretion was ejected in spurts, owing doubtless to contractions of the muscular walls of the larger bile-ducts. But though continuously formed within the liver-cells, the flow of bile is subject to considerable variations. According to most observers the activity of secretion is definitely connected with the period of digestion. Somewhere from the third to the fifth hour after the beginning of digestion there is a very marked acceleration of the flow, and a second maximum at a later period, ninth to tenth hour (Hoppe-Seyler), has been observed in dogs. The mechanism controlling the accelerated flow during the third to the fifth hour is not perfectly understood. It would seem to be correlated with the digestive changes occurring in the intestine, but whether the relationship is of the nature of a reflex nervous act, or whether it depends on increased blood-flow through the organ or upon some action of the absorbed products of secretion remains to be determined. It has been shown that the presence of bile in the blood acts as a stimulus to the liver-cells, and it is highly probable that the absorption of bile from the intestine which occurs during digestion serves to accelerate the secretion; but this circumstance obviously does not account for the marked increase observed in animals with biliary fistulas, since in these cases the bile does not reach the intestine at all. Therapeutically various substances have been stated by different authors to act as true cholagogues—that is, to stimulate the

<sup>1</sup> *Hermann's Handbuch der Physiologie*, Bd. v. Thl. 1, S. 253.

secretion of bile. Of these substances the one whose action is most undoubted is bile itself or the bile acids. When given as dried bile, in the form of pills, a marked increase in the flow is observed.<sup>1</sup>

**Relation of the Secretion of Bile to the Blood-flow in the Liver.—**

Numerous experiments have shown that the quantity of bile formed by the liver varies more or less directly with the quantity of blood flowing through the organ. The liver-cells receive blood from two sources, the portal vein and the hepatic artery. The supply from both these sources is probably essential to the perfectly normal activity of the cells, but it has been shown that bile continues to be formed, for a time at least, when either the portal or the arterial supply is occluded. However, there can be little doubt that the material actually utilized by the liver-cells in the formation of their external and internal secretions is brought to them mainly by the portal vein, and that variations in the quantity of this supply influences directly the amount of bile produced. Thus, occlusion of some of the branches of the portal vein diminishes the secretion; stimulation of the spinal cord diminishes the secretion, since, owing to the large vascular constriction produced thereby in the abdominal viscera, the quantity of blood in the portal circulation is reduced; section of the spinal cord also diminishes the flow of bile or may even stop it altogether, since the result of such an operation is a general paralysis of vascular tone and a general fall of blood-pressure and velocity; stimulation of the cut splanchnic nerves diminishes the secretion because of the strong constriction of the blood-vessels of the abdominal viscera and the resulting diminution of the quantity of the blood in the portal circulation; section of the splanchnics alone, however, is said to increase the quantity of bile, in dogs, since in this case the paralysis of vascular tone is localized in the abdominal viscera. The effect of such a local dilatation of the blood-vessels would be to diminish the resistance along the intestinal paths, and thus lead to a greater flow of blood to that area and the portal circulation.

In all these cases one might suppose that the greater or less quantity of bile formed depended only on the blood-pressure in the capillaries of the liver lobules—that so far at least as the water of the bile is concerned it is produced by a process of filtration and rises and falls with the blood-pressure. That this simple mechanical explanation is not sufficient seems to be proved by the fact that the pressure of bile within the bile-ducts, although comparatively low, may exceed that of the blood in the portal vein.

**The Existence of Secretory Nerves to the Liver.**—The numerous experiments that have been made to ascertain whether or not the secretion of bile is under the direct control of secretory nerves have given unsatisfactory results. The experiments are difficult, since stimulation of the nerves supplying the liver, such as the splanchnic, is accompanied by vaso-motor changes which alter the blood-flow to the organ and thus introduce a factor that in itself influences the amount of the secretion. So far as our actual knowledge goes, the physiological evidence is against the existence of secretory nerve-

<sup>1</sup> *Journal of Experimental Medicine*, 1897, vol. ii. p. 42.



fibres controlling the formation of bile. On the other hand, there are some experiments,<sup>1</sup> although they are not perfectly conclusive, which indicate that the glycogen formation within the liver-cells is influenced by a special set of *glyco-vascular* nerve-fibres. This fact, however, does not bear directly upon the formation of bile.

**Motor Nerves of the Bile-vessels.**—Doyon<sup>2</sup> has recently shown that the gall-bladder as well as the bile-ducts is innervated by a set of nerve-fibres comparable in their general action to the vaso-constrictor and vaso-dilator fibres of the blood-vessels. According to this author, stimulation of the peripheral end of the cut splanchnics causes a contraction of the bile-ducts and gall-bladder, while stimulation of the central end of the same nerve, on the contrary, brings about a reflex dilatation. Stimulation of the central end of the vagus nerve causes a contraction of the gall-bladder and at the same time an inhibition of the sphincter muscle closing the opening of the common bile-duct into the duodenum. These facts need confirmation, perhaps, on the part of other observers, although they are in accord with what is known of the actual movement of the bile-stream. The ejection of bile from the gall-bladder into the duodenum is produced by a contraction of the gall-bladder, and it is usually believed that this contraction is brought about reflexly from some sensory stimulation of the mucous membrane of the duodenum or stomach. The result of the experiments made by Doyon would indicate that the afferent fibres of this reflex pass upward in the vagus, while the efferent fibres to the gall-bladder run in the splanchnics and reach the liver through the semilunar plexus.

**Normal Mechanism of the Bile-secretion.**—Bearing in mind the fact that our knowledge of the secretion of bile is in many respects incomplete, and that any description of the act is therefore partly conjectural, we might picture the processes concerned in the secretion and ejection of bile as follows: The bile is steadily formed by the liver-cells and turned out into the bile-capillaries; its quantity varies with the quantity and composition of the blood flowing through the liver, but the formation of the secretion depends upon the activities taking place in the liver-cells, and these activities are independent of direct nervous control. During the act of digestion the formation of bile is increased, owing probably to a greater blood-flow through the organ and to the generally increased metabolic activity of the liver-cells occasioned by the inflow of the absorbed products of digestion. The bile after it gets into the bile-ducts is moved onward partly by the accumulation of new bile from behind, the secretory force of the cells, and partly by the contractions of the walls of the bile-vessels. It is stored in the gall-bladder, and at intervals during digestion is forced into the duodenum by a contraction of the muscular walls of the bladder, the process being aided by the simultaneous relaxation of a sphincter-like layer of muscle that normally occludes the bile-duct at its opening into the intestine; both these last acts are under the control of a nervous reflex mechanism.

<sup>1</sup> Morat and Dufourt: *Archives de Physiologie*, 1894, p. 371.

<sup>2</sup> *Archives de Physiologie*, 1894, p. 19; see also Oddi: *Arch. ital. de Biologie*, t. xxii., cvi.

In a very interesting research by Bruno<sup>1</sup> it has been shown that the actual passage of bile into the intestine is occasioned, reflexly no doubt, by the passage of the chyme from stomach to intestine. As long as the stomach is empty no bile flows into the duodenum; the flow commences when the stomach begins to empty its contents into the intestine, and ceases as soon as this process is completed. The author endeavored to ascertain the substances in the chyme that serve as the stimulus in this reaction. As far as his experiments go, they show that fats and the digested products of proteids (peptones and proteoses) are the most efficient stimuli. Acids, alkalies, and starch or the substances formed from it during salivary digestion are ineffective. Presumably the fats and the products of proteid digestion act on the sensory fibres of the duodenal membrane.

**Effect of Complete Occlusion of the Bile-duct.**—It is an interesting fact that when the flow of bile is completely prevented by ligation of the bile-duct, the stagnant liquid is not reabsorbed by the blood directly, but by the lymphatics of the liver. The bile-pigments and bile-acids in such cases may be detected in the lymph as it flows from the thoracic duct. In this way they get into the blood, producing a jaundiced condition. The way in which the bile gets from the bile-ducts into the hepatic lymphatics is not definitely known, but possibly it is due to a rupture, caused by the increased pressure, at some point in the course of the delicate bile-capillaries.

#### KIDNEY.

**Histology.**—The kidney is a compound tubular gland. The constituent uriniferous tubules composing it may be roughly separated into a secreting part comprising the capsule, convoluted tubes, and loop of Henle, and a collecting part, the so-called straight collecting-tube, the epithelium of which is assumed not to have any secretory function. Within the secreting part the epithelium differs greatly in character in different regions; its peculiarities may be referred to briefly here so far as they seem to have a physiological bearing, although for a complete description reference must be made to some work on Histology.

The arrangement of the glandular epithelium in the capsule with reference to the blood-vessels of the glomerulus is worthy of special attention. It will be remembered that each Malpighian corpuscle consists of two principal parts, a tuft of blood-vessels, the glomerulus, and an enveloping expansion of the uriniferous tubule, the capsule. The glomerulus is a remarkable structure (see Fig. 65, A). It consists of a small afferent artery which after entering the glomerulus breaks up into a number of capillaries, which, though twisted together, do not anastomose. These capillaries unite to form a single efferent vein of a smaller diameter than the afferent artery. The whole structure, therefore, is not an ordinary capillary area, but a *rete mirabile*, and the physical factors are such that within the capillaries of the rete there must be a greatly diminished velocity of the blood-stream, owing to the great increase

<sup>1</sup> *Archives des sciences biologiques*, 1899, t. vii. p. 87.



in the width of the stream-bed, and a high blood-pressure as compared with ordinary capillaries. Surrounding this glomerulus is the double-walled capsule. One wall of the capsule is closely adherent to the capillaries of the glomerulus; it not only covers the structure closely, but dips into the interior between the small lobules into which the glomerulus is divided. This layer of the capsule is composed of flattened endothelial-like cells, the glomerular epithelium, to which great importance is now attached in the formation of the secretion. It will be noticed that between the interior of the blood-vessels of the glomerulus and



FIG. 65.—Portions of the various divisions of the uriniferous tubules drawn from sections of human kidney: *A*, Malpighian body; *z*, squamous epithelium lining the capsule and reflected over the glomerulus; *y*, *z*, afferent and efferent vessels of the tuft; *z*, nuclei of capillaries; *n*, constricted neck marking passage of capsule into convoluted tubule; *B*, proximal convoluted tubule; *C*, irregular tubule; *D* and *F*, spiral tubules; *E*, ascending limb of Henle's loop; *G*, straight collecting tubule (Piersol).

the cavity of the capsule, which is the beginning of the uriniferous tubule, there are interposed only two very thin layers, namely, the epithelium of the capillary wall and the glomerular epithelium. The apparatus would seem to afford most favorable conditions for filtration of the liquid parts of the blood. The epithelium clothing the convoluted portions of the tubule, including under this designation the so-called irregular and spiral portions and the loop of Henle, is of a character quite different from that of the glomerular epithelium (Fig. 65, *B*, *C*, *D*, *E*, *F*, *G*). The cells, speaking generally, are cuboidal or cylindrical, protoplasmic, and granular in appearance; on the side toward the basement membrane they often show a peculiar striation, while on the lumen side the extreme periphery presents a compact border which in some cases shows a cilia-like striation. These cells have the general appearance of active secretory structures, and recent theories of urinary secretion attribute this importance to them.

**Composition of Urine.**—The chemical composition of the urine is very complex, as we should expect it to be when we remember that it contains most of the end-products of the varied metabolism of the body, its importance in this respect being greater than the other excretory organs such as the lungs, skin, and intestine. The secretion is a yellowish liquid which in carnivorous animals and in man has normally an acid reaction, owing to the presence of acid

salts (acid sodium and acid calcium phosphate), and an average specific gravity of 1017 to 1020. The quantity formed in twenty-four hours is about 1200 to 1700 cubic centimeters. In the very young the amount of urine formed is proportionately much greater than in the adult. The normal urine contains about 3.4 to 4 per cent. of solid matter, of which over half is organic material. Among the important organic constituents of the urine are the following: urea, uric acid, hippuric acid, xanthin, hypoxanthin, guanin, creatinin and aromatic oxy-acids (para-oxyphenyl propionic acid and para-oxyphenyl acetic acid, as simple salts or combined with sulphuric acid); phenol, paracresol, pyrocatechin and hydrochinon, these four substances being combined with sulphuric or glycuronic acid; indican or indoxyl sulphuric acid; skatol sulphuric acid; oxalic acid; sulphocyanides, etc. These and other organic constituents occurring under certain conditions of health or disease in various animals, are of the greatest importance in enabling us to follow the metabolism of the body. Something as to their origin and significance will be found in the section on Nutrition, while their purely chemical relations are described in the section on Chemistry.

Among the inorganic constituents of the urine may be mentioned sodium chloride, sulphates, phosphates of the alkalies and alkaline earths, nitrates, and carbon dioxide gas partly in solution and partly as carbonate. In this section we are concerned only with the general mechanism of the secretion of urine, and in this connection have to consider mainly the water and soluble inorganic salts and the typical nitrogenous excreta, namely, urea and uric acid.

**The Secretion of Urine.**—The kidneys receive a rich supply of nerve-fibres, but most histologists have been unable to trace any connection between these fibres and the epithelial cells of the kidney tubules. Berkley<sup>1</sup> has, however, described nerve-fibres passing through the basement membrane and ending between the secretory cells.

The majority of purely physiological experiments upon direct stimulation of the nerves going to the kidney are adverse to the theory of secretory fibres, the marked effects obtained in these experiments being all explicable by the changes produced in the blood-flow through the organ. Two general theories of urinary secretion have been proposed. Ludwig held that the urine is formed by the simple physical processes of filtration and diffusion. In the glomeruli the conditions are most favorable to filtration, and he supposed that in these structures water filtered through from the blood, carrying with it not only the inorganic salts, but also the specific elements (urea) of the secretion. There was thus formed at the beginning of the uriniferous tubules a complete but diluted urine, and in the subsequent passage of this liquid along the convoluted tubes it became concentrated by diffusion with the lymph surrounding the outside of the tubules. So far as the latter part of this theory is concerned it has not been supported by actual experiments; recent histological work (see below) seems to indicate that the epithelial cells of the convoluted tubules have a

<sup>1</sup> *The Johns Hopkins Hospital Bulletin*, vol. iv., No. 28, p. 1.



distinct secretory function, and that they give material to the secretion rather than take from it.

Bowman's theory of urinary secretion, which has since been vigorously supported and extended by Heidenhain, was based apparently mainly on histological grounds. It assumes that in the glomeruli water and inorganic salts are produced, while the urea and related bodies are eliminated through the activity of the epithelial cells in the convoluted tubes.

*Elimination of Urea and Related Bodies.*—Numerous facts have been discovered which tend to support the latter part of Bowman's theory—namely, the participation of the cells of the convoluted tubules in the secretion of the specific nitrogenous elements. In birds the main nitrogenous element of the secretion is uric acid instead of urea, and it is possible, owing to the small solubility of the urates, to see them as solid deposits in microscopic sections of the kidney. When the ureters are ligated the deposition of the urates in the kidney may become so great as to give the entire organ a whitish appearance. Nevertheless histological examination of a kidney in this condition shows that the urates are found always in the tubes and never in the Malpighian corpuscles. From this result we may conclude that the uric acid is eliminated through the epithelial cells of the tubes. Heidenhain has shown by a striking series of experiments that the cells of the tubes possess an active secretory power. In these experiments a solution of indigo-carmin was injected into the circulation of a living animal after its spinal cord had been cut to reduce the blood-pressure and therefore the rapidity of the secretion. After a certain interval the kidneys were removed and the indigo-carmin precipitated *in situ* in the kidney by injecting alcohol into the blood-vessels. It was found that the pigment granules were deposited in the convoluted tubes, but never in the Malpighian corpuscles.

Still further proof of definite secretory functions on the part of the cells of the tubules is given by the results of recent histological work upon the changes in the cells during activity. Van der Stricht,<sup>1</sup> Disse,<sup>2</sup> and Traubst<sup>3</sup> describe definite morphological changes in the epithelial cells of the convoluted tubes and ascending loop of Henle which they connect with the functional activity of the cells. The details of the descriptions differ, but the authors agree in finding that the material of the secretion collects in the interior of the cell to form a vesicle which is afterward discharged into the lumen of the cell. According to Disse the inactive cells are small and granular, and toward the lumen show a striated border of minute processes, while the lumen of the tube is relatively wide. As the fluid secretion accumulates in the cells it may be distinguished as a clear vesicular area near the nucleus. The cells enlarge and project toward the lumen, which becomes smaller; the striated border disappears. Finally the swollen cells fill the entire canal, and the liquid secre-

<sup>1</sup> *Comptes rendus*, 1891, and *Travail du Laboratoire d'Histologie de l'Université de Gand*, 1892.

<sup>2</sup> *Referate und Beiträge zur Anatomie und Entwicklungsgeschichte* (anatomische Hefte, Merkel and Bonnet, 1893).

<sup>3</sup> *Archives italiennes de Biologie*, 1898, t. 30, p. 426.

tion is emptied from the cells by filtration. Van der Stricht believes that the vesicles rupture and thus empty into the lumen. In longitudinal sections various stages in the process may be seen scattered along the length of a single tubule.

*Secretion of the Water and Salts.*—There seems to be no question that the elimination of water together with inorganic salts, and probably still other soluble constituents, takes place chiefly through the glomerular epithelium. This supposition is made in both the general theories that have been mentioned. It has, however, long been a matter of controversy, in this as in other glands, whether the water is produced by simple filtration or whether the glomerular epithelium takes an active part of some character in setting up the stream of water. The problem is perhaps simpler in this case than in the salivary glands, since the direct participation of secretory nerves in the process is excluded. On the filtration theory the quantity of urine should vary directly with the blood-pressure in the glomerulus. This relationship has been accepted as a crucial test of the validity of the filtration theory, and numerous experiments have been made to ascertain whether it invariably exists. Speaking broadly, any general rise of blood-pressure in the aorta will occasion a greater blood-flow and greater pressure in the glomerular vessels provided the kidney arteries themselves are not simultaneously constricted to a sufficient extent to counteract this favorable influence; whereas a general fall of pressure should have the opposite influence both on pressure and velocity of flow. It has been shown experimentally that if the general arterial pressure falls below 40 or 50 millimeters of mercury, as may happen after section of the spinal cord in the cervical region, the secretion of the urine will be greatly slowed, or suspended completely. Constriction of the small arteries in the kidney, whether effected through its proper vaso-constrictor nerves or by partially clamping its arteries, causes a diminution in the secretion and at the same time in all probability a fall of pressure within the glomeruli and a diminution in the total flow of blood. On the other hand, dilatation of the arteries of the kidney, whether produced through its vaso-dilator fibres or by section or inhibition of its constrictor fibres, augments the flow of urine and at the same time probably increases the pressure within the glomerular capillaries, and also the total quantity of blood flowing through them in a unit of time. From these and other experimental facts it is evident that the amount of secretion and the amount of pressure within the glomerular vessels do often vary together, and this relationship has been used to prove that the water of the secretion is obtained by filtration from the blood-plasma. But it will be observed that the quantity of secretion varies not only with the pressure of the blood within the glomeruli, but also with the quantity of blood flowing through them. Heidenhain has insisted that it is this latter factor and not the intracapillary pressure which determines the quantity of water secreted. He believes that the glomerular epithelial cells possess the property of actively secreting water, and that they are not simply passive filters; that the formation, in other words, is not a simple mechanical process, but a more complex



one depending upon the living structure and properties of the epithelial cells. In support of this view he quotes the fact that partial compression of the renal veins quickly slows or stops altogether the flow of urine. Compression of the veins should raise the pressure within the vessels of the glomeruli, and upon the filtration hypothesis should increase rather than diminish the secretion. It has been shown also that if the renal artery is compressed for a short time so as to completely shut off the blood-flow to the kidney the secretion is not only suspended during the closure of the arteries but for a long time after the circulation is re-established. According to Tiegerstedt, if the renal artery is ligated for only half a minute the activity of the kidney is suspended for three-quarters of an hour. This fact is difficult to understand if the glomerular epithelium is regarded simply as a filtering membrane, but it is explicable upon the hypothesis that the epithelial cells are actively concerned in the production of the water.

The uncertainty as to the mechanism of production of the water and salts renders it difficult to give a theoretical explanation of the action of diuretics. Various saline substances, such as NaCl and KNO<sub>3</sub>, increase the flow of urine. According to Starling,<sup>1</sup> these substances increase the bulk of water in the blood by drawing water from the tissues. A condition of hydropic plethora ensues, causing a greater volume of blood in the kidney capillaries and a rise of capillary pressure, conditions that favor greater filtration and account in part for the increased amount of urine. Experiments seem to show, however, that the condition of hydropic plethora passes off before the increased secretion of urine ceases, so that the diuretic action of the salts is not due to this factor alone. The adherents of the filtration theory assume that in addition the salts cause a vaso-dilatation in the kidney, and thus produce a rise in blood-pressure in the glomeruli. According to the other point of view, these substances may be considered as having a specific stimulating effect upon the glomerular epithelium. So the action of caffeine may be referred either to a specific action<sup>2</sup> on the secreting cells or possibly to an indirect effect exerted through the circulation of the kidney. It seems clear that at present we are not justified in asserting more than that the glomeruli control in some way the production of the water and salts of the secretion. The extent of the activity seems to be correlated with the quantity of blood flowing through the glomeruli.

It must be borne in mind, however, that some water and probably also some of the inorganic salts are secreted at other parts of the tubule along with the nitrogenous wastes. It is of interest to add that the most important of the abnormal constituents of the urine under pathological conditions, such as the albumin in albuminuria, the hæmoglobin in hæmoglobinuria, and the sugar in glycosuria, seem likewise to escape from the blood into the kidney tubules through the glomerular epithelium.

<sup>1</sup> *Journal of Physiology*, 1899, vol. 24, p. 317.

<sup>2</sup> See Von Schroeder: *Archiv. für exper. Pathologie und Pharmacol.*, Bd. xxiv. S. 85; and Dreser, *Ibid.*, 1892, Bd. xxix. S. 303.

The normal stimulus to the epithelial cells of the convoluted tubules, using the term convoluted to include the actively secreting parts, seems to be the presence of urea and related substances in the blood (lymph). That the elimination of the urea is not a simple act of diffusion seems to be clearly shown by the fact that its percentage in the blood is much less than in the urine. In some way the urea is selected from the blood and passed into the lumen of the tubule, and although we have microscopic evidence that this process involves active changes in the substance of the cells, there is no adequate theory of the nature of the force which attracts the urea from the surrounding lymph. The whole process must be rapidly effected by the cell, since there is normally no heaping up of urea in the kidney-cells; the material is eliminated into the tubules as quickly as it is received from the blood. The rate of elimination increases normally with the increase in the urea in the blood, as would be expected upon the assumption that the urea itself acts as the physiological stimulus to the epithelial cells.

**The Blood-flow through the Kidneys.**—It will be seen from the discussion above that, other conditions remaining the same, the secretion of the kidney varies with the quantity of blood flowing through it. It is therefore important at this point to refer briefly to the nature and especially the regulation of the blood-flow through this organ, although the same subject is referred to in connection with the general description of vaso-motor regulation (see Circulation). It has been shown by Landerlgren<sup>1</sup> and Tiegerstedt that the kidney is a very vascular organ, at least when it is in strong functional activity such as may be produced by the action of diuretics. They estimate that in a minute's time, under the action of diuretics, an amount of blood flows through the kidney equal to the weight of the organ; this is an amount from four to nineteen times as great as occurs in the average supply of the other organs in the systemic circulation. Taking both kidneys into account, their figures show that (in strong diuresis) 5.6 per cent. of the total quantity of blood sent out of the left heart in a minute may pass through the kidneys, although the combined weight of these organs makes only 0.56 per cent. of that of the body.

The nature of the supply of vaso-motor nerves to the kidney and the conditions which bring them into activity are fairly well known, owing to the useful invention of the oncometer by Roy.<sup>2</sup> This instrument is in principle a plethysmograph especially modified for use upon the kidney of the living animal. It is a kidney-shaped box of thin brass made in two parts, hinged at the back, and with a clasp in front to hold them together. In the interior of the box thin peritoneal membrane is so fastened to each half that a layer of olive oil may be placed between it and the brass walls. There is thus formed in each half a soft pad of oil upon which the kidney rests. When the kidney, freed as far as possible from fat and surrounding connective tissue, but with the blood-vessels and nerves entering at the hilus entirely uninjured, is laid in

<sup>1</sup> *Skandinavisches Archiv für Physiologie*, 1892, Bd. iv. S. 241.

<sup>2</sup> See Cohnheim and Roy: *Virchow's Archiv*, 1883, Bd. xcii. S. 424.



one-half of the oncometer, and the other half is shut down upon it and tightly fastened, the organ is surrounded by oil in a box which is liquid-tight at every point except one, where a tube is led off to some suitable recorder such as a tambour. Under these conditions every increase in the volume of the kidney will cause a proportional outflow of oil from the oncometer, which will be measured by the recorder, and every diminution in volume will be accompanied by a reverse change. At the same time the flow of urine during these changes can be determined by inserting a cannula into the ureter and measuring directly the outflow of urine. By this and other means it has been shown that the kidney receives a rich supply of vaso-constrictor nerve-fibres that reach it between and round the entering blood-vessels. These fibres emerge from the spinal cord chiefly in the lower thoracic spinal nerves (tenth to thirteenth in the dog), pass through the sympathetic system, and reach the organ as non-medullated fibres. Stimulation of these nerves causes a contraction of the small arteries of the kidney, a shrinkage in volume of the whole organ as measured by the oncometer, and a diminished secretion of urine. When, on the other hand, these constrictor fibres are cut as they enter the hilus of the kidney, the arteries are dilated on account of the removal of the tonic action of the constrictor fibres, the organ enlarges, and a greater quantity of blood passes through it, since the resistance to the blood-flow is diminished while the general arterial pressure in the aorta remains practically the same. Along with this greater flow of blood there is a marked increase in the secretion of urine.

Under normal conditions we must suppose that these fibres are brought into play to a greater or less extent by reflex stimulation, and thus serve to control the blood-flow through the kidney and thereby influence its functional activity. It has been shown, too, that the kidney receives vaso-dilator nerve-fibres, that is, fibres which when stimulated directly or reflexly cause a dilatation of the arteries, and therefore a greater flow of blood through the organ. According to Bradford,<sup>1</sup> these fibres emerge from the spinal cord mainly in the anterior roots of the eleventh, twelfth, and thirteenth spinal nerves. Under normal conditions these fibres are probably thrown into action by reflex stimulation and lead to an increased functional activity. It will be seen, therefore, that the kidneys possess a local nervous mechanism through which their secretory activity may be increased or diminished by corresponding alterations in the blood-supply. So far as is known, this is the only way in which the secretion in the kidneys can be directly affected by the central nervous system. It should be borne in mind, also, that the blood-flow through the kidneys, and therefore their secretory activity, may be affected by conditions influencing general arterial pressure. Conditions such as asphyxia, strychnin-poisoning, or painful stimulation of sensory nerves, which cause a general vaso-constriction, influence the kidney in the same way, and tend, therefore, to diminish the flow of blood through it; while conditions which lower general arterial pressure, such as general vascular dilatation of the skin

<sup>1</sup> *Journal of Physiology*, 1889, vol. x. p. 358.

vessels, may also depress the secretory action of the kidney by diminishing the amount of blood flowing through it.

In what way any given change in the vascular conditions of the body will influence the secretion of the kidney depends upon a number of factors, and their relations to one another; but any change which will increase the difference in pressure between the blood in the renal artery and the renal vein will tend to augment the flow of blood unless it is antagonized by a simultaneous constriction in the small arteries of the kidney itself. On the contrary, any vascular dilatation of the vessels in the kidney will tend to increase the blood-flow through it unless there is at the same time such a general fall of blood-pressure as is sufficient to lower the pressure in the renal artery and reduce the driving force of the blood to an extent that more than counteracts the favorable influence of diminished resistance in the small arteries.

**Movements of the Ureter and the Bladder.**—(See Micturition, p. 389.)

#### E. CUTANEOUS GLANDS; INTERNAL SECRETIONS.

The sebaceous glands, sweat-glands, and mammary glands are all true epidermal structures, and may therefore be conveniently treated together.

**Sebaceous Secretion.**—The sebaceous glands are simple or compound alveolar glands found over the cutaneous surface usually in association with the hairs, although in some cases they occur separately, as, for instance, on the prepuce and glans penis, and on the lips. When they occur with the hairs the short duct opens into the hair-follicle, so that the secretion is passed out upon the hair near the point where it projects from the skin. The alveoli are filled with cuboidal or polygonal epithelial cells, which are arranged in several layers. Those nearest the lumen of the gland are filled with fatty material. These cells are supposed to be cast off bodily, their detritus going to form the secretion. New cells are formed from the layer nearest the basement membrane, and thus the glands continue to produce a slow but continuous secretion. The sebaceous secretion, or sebum, is an oily semi-liquid material that sets upon exposure to the air to a cheesy mass, as is seen in the comedones or pimples which so frequently occur upon the skin from occlusion of the opening of the ducts. The exact composition of the secretion is not known. It contains fats and soaps, some cholesterin, albuminous material, part of which is a nucleo-albumin often described as a casein, remnants of epithelial cells, and inorganic salts. The cholesterin occurs in combination with a fatty acid and is found in especially large quantities in sheep's wool, from which it is extracted and used commercially under the name of lanolin. The sebaceous secretion from different places, or in different animals, is probably somewhat variable in composition as well as in quantity. The secretion of the prepuce is known as the *smegma preputii*; that of the external auditory meatus, mixed with the secretion of the neighboring sweat-glands or ceruminous glands, forms the well-known ear-wax or *cerumen*. The secretion in this place contains a reddish pigment of a bitterish-sweet taste, the composition of which has not been investigated. Upon the skin of the newly-born the sebaceous ma-



terial is accumulated to form the *vernix caseosa*. The well-known uropygial gland of birds is homologous with the mammalian sebaceous glands, and its secretion has been obtained in sufficient quantities for chemical analysis. Physiologically it is believed that the sebaceous secretion affords a protection to the skin and hairs. Its oily character doubtless serves to protect the hairs from becoming too brittle, or, on the other hand, from being too easily saturated with external moisture. In this way it probably aids in making the hairy coat a more perfect protection against the effect of external changes of temperature. Upon the surface of the skin also it forms a thin protective layer that tends to prevent undue loss of heat from evaporation, and possibly is important in other ways in maintaining the physiological integrity of the external surface.

**Sweat.**—The sweat or perspiration is a secretion of the sweat-glands. These latter structures are found over the entire cutaneous surface except in the deeper portions of the external auditory meatus. They are particularly abundant upon the palms of the hands and the soles of the feet. Krause estimates that their total number for the whole cutaneous surface is about two millions. In man they are formed on the type of simple tubular glands; the terminal portion contains the secretory cells, and at this part the tube is usually coiled to make a more or less compact knot, thus increasing the extent of the secreting surface. The larger ducts have a thin muscular coat of involuntary tissue that may possibly be concerned in the ejection of the secretion. The secretory cells in the terminal portion are columnar in shape, they possess a granular cytoplasm and are arranged in a single layer. The amount of secretion formed by these glands varies greatly, being influenced by the condition of the atmosphere as regards temperature and moisture, as well as by various physical and psychical states, such as exercise and emotions. The average quantity for twenty-four hours is said to vary between 700 and 900 grams, although this amount may be doubled under certain conditions.

According to an interesting paper by Schierbeck,<sup>1</sup> the average quantity of sweat in twenty-four hours may amount to 2 to 3 liters in a person clothed, and therefore with an average temperature of 32° C. surrounding the skin. This author states that the amount of sweat given off from the skin in the form of insensible perspiration increases proportionately with the temperature until a certain critical point is reached (about 33° C. in the person investigated), when there is a marked increase in the water eliminated, the increase being simultaneous with the formation of visible sweat. At the same time there is a more marked and sudden increase in the CO<sub>2</sub> eliminated from the skin, from 8 grams to 20 grams in twenty-four hours. It is possible that the sudden increase in CO<sub>2</sub> is an indication of greater metabolism in the sweat-glands in connection with the formation of visible sweat.

**Composition of the Secretion.**—The precise chemical composition of sweat is difficult to determine, owing to the fact that as usually obtained it is liable

<sup>1</sup> *Archiv für Anatomie und Physiologie* (Physiol. Abtheil.), 1893, S. 116.

to be mixed with the sebaceous secretion. Normally it is a very thin secretion of low specific gravity (1004) and an alkaline reaction, although when first secreted the reaction may be acid owing to admixture with the sebaceous material. The larger part of the inorganic salts consists of sodium chloride. Small quantities of the alkaline sulphates and phosphates are also present. The organic constituents, though present in mere traces, are quite varied in number. Urea, uric acid, creatinin, aromatic oxy-acids, ethereal sulphates of phenol and skatol, and albumin, are said to occur when the sweating is profuse. Argutinsky has shown that after the action of vapor-baths, and as the result of muscular work, the amount of urea eliminated in this secretion may be considerable (see p. 360). Under pathological conditions involving a diminished elimination of urea through the kidneys it has been observed that the amount found in the sweat is markedly increased, so that crystals of it may be deposited upon the skin. Under perfectly normal conditions, however, it is obvious that the organic constituents are of minor importance. The main fact to be considered in the secretion of sweat is the formation of water.

*Secretory Fibres to the Sweat-glands.*—Definite experimental proof of the existence of sweat-nerves was first obtained by Goltz<sup>1</sup> in some experiments upon stimulation of the sciatic nerve in cats. In the cat and dog, in which sweat-glands occur on the balls of the feet, the presence of sweat-nerves may be demonstrated with great ease. Electrical stimulation of the peripheral end of the divided sciatic nerve, if sufficiently strong, will cause visible drops of sweat to form on the hairless skin of the balls of the feet. When the electrodes are kept at the same spot on the nerve and the stimulation is maintained the secretion soon ceases, but this effect seems to be due to a temporary injury of some kind to the nerve-fibres at the point of stimulation, and not to a genuine fatigue of the sweat-glands or the sweat-fibres, since moving the electrodes to a new point on the nerve farther toward the periphery calls forth a new secretion. The secretion so formed is thin and limpid, and has a marked alkaline reaction. The anatomical course of these fibres has been worked out in the cat with great care by Langley.<sup>2</sup> He finds that for the hind feet they leave the spinal cord chiefly in the first and second lumbar nerves, enter the sympathetic chain, and emerge from this as non-medullated fibres in the gray rami proceeding from the sixth lumbar to the second sacral ganglion, but chiefly in the seventh lumbar and first sacral, and then join the nerves of the sciatic plexus. For the fore feet the fibres leave the spinal cord in the fourth to the tenth thoracic nerves, enter the sympathetic chain, pass upward to the first thoracic ganglion, whence they are continued as non-medullated fibres that pass out of this ganglion by the gray rami communicating with the nerves forming the brachial plexus. The action of the nerve-fibres upon the sweat-glands cannot be explained as an indirect effect—for instance, as a result of a variation in the blood-flow. Experiments have repeatedly shown that, in the cat, stimulation of the sciatic still calls forth a secretion after the

<sup>1</sup> *Archiv für die gesammte Physiologie*, 1875, Bd. xi. S. 71.

<sup>2</sup> *Journal of Physiology*, 1891, vol. xii. p. 347.



blood has been shut off from the leg by ligation of the aorta, or indeed after the leg has been amputated for as long as twenty minutes. So in human beings it is known that profuse sweating may often accompany a pallid skin, as in terror or nausea, while on the other hand the flushed skin of fever is characterized by the absence of perspiration. There seems to be no doubt at all that the sweat-nerves are genuine secretory fibres, causing a secretion in consequence of a direct action on the cells of the sweat-glands. In accordance with this physiological fact histological work has demonstrated that special nerve-fibres are supplied to the glandular epithelium. According to Arnstein<sup>1</sup> the terminal fibres form a small branching varicose ending in contact with the epithelial cells. The sweat-gland may be made to secrete in many ways other than by direct artificial excitation of the sweat-fibres; for example, by external heat, dyspnoea, muscular exercise, strong emotions, and by the action of various drugs such as pilocarpin, muscarin, strychnin, nicotin, picrotoxin, and physostigmin. In all such cases the effect is supposed to result from an action on the sweat-fibres, either directly on their terminations, or indirectly upon their cells of origin in the central nervous system. In ordinary life the usual cause of profuse sweating is a high external temperature or muscular exercise. With regard to the former it is known that the high temperature does not excite the sweat-glands immediately, but through the intervention of the central nervous system. If the nerves going to a limb be cut, exposure of that limb to a high temperature does not cause a secretion, showing that the temperature change alone is not sufficient to excite the gland or its terminal nerve-fibres. We must suppose, therefore, that the high temperature acts upon the sensory cutaneous nerves, possibly the heat-fibres, and reflexly stimulates the sweat-fibres. Although external temperature does not directly excite the glands, it should be stated that it affects their irritability either by direct action on the gland-cells or upon the terminal nerve-fibres. At a sufficiently low temperature the cat's paw does not secrete at all, and the irritability of the glands is increased by a rise of temperature up to about 45° C.

Dyspnoea, muscular exercise, emotions, and many drugs affect the secretion, probably by action on the nerve-centres. Pilocarpin, on the contrary, is known to stimulate the endings of the nerve-fibres in the glands, while atropin has the opposite effect, completely paralyzing the secretory fibres.

*Sweat-centres in the Central Nervous System.*—The fact that secretion of sweat may be occasioned by stimulation of afferent nerves or by direct action upon the central nervous system, as in the case of dyspnoea, implies the existence of physiological centres controlling the secretory fibres. The precise location of the sweat-centre or centres has not, however, been satisfactorily determined. Histologically and anatomically the arrangement of the sweat-fibres resembles that of the vaso-constrictor fibres, and, reasoning from analogy, one might suppose the existence of a general sweat-centre in the medulla comparable to the vaso-constrictor centre, but positive evidence of the existence of such

<sup>1</sup> *Anatomischer Anzeiger*, 1895, Bd. x.

an arrangement is lacking. It has been shown that when the medulla is separated from the cord by a section in the cervical or thoracic region the action of dyspnoea, or of various sudorific drugs supposed to act on the central nervous system, may still cause a secretion. On the evidence of results of this character it is assumed that there are spinal sweat-centres, but whether these are few in number or represent simply the various nuclei of origin of the fibres to different regions is not definitely known. It is possible that in addition to these spinal centres there is a general regulating centre in the medulla.

#### MAMMARY GLANDS.

The mammary glands are undoubtedly epidermal structures comparable in development to the sweat- or the sebaceous glands. Whether they are to be homologized with the sweat- or with the sebaceous glands is not clearly determined. In most animals they are compound alveolar glands, and their acinous structure and the rich albuminous and fatty constituents of their secretion would seem to suggest a relationship to the sebaceous glands. But the histological structure of the alveolus with its single layer of epithelium points rather to a connection with the sweat-glands. Whatever may have been their exact origin in the primitive mammalia, there seems to be no question that they were derived in the first place from some of the ordinary skin-glands which at first simply opened, without a distinct mamma or nipple, on a definite area of the skin, as is seen now in the case of the monotremes. Later in the phylogenetic history of the gland the separate ducts united to form one or more larger ones, and these opened to the exterior upon the protrusion of the skin known as the nipple. The number and position of the glands vary much in the different mammalia. In man they are found in the thoracic region and are normally two in number. The milk-ducts do not unite to form a single canal, but form a group of fifteen to twenty separate systems, each of which opens separately upon the surface of the nipple. Before pregnancy the secreting alveoli are incompletely formed, but during pregnancy and at the time lactation begins the formation of the alveoli is greatly accelerated by proliferation of the epithelial cells.

**Composition of the Secretion.**—The general appearance and composition of the milk are well known. Microscopically milk consists of a liquid portion, or plasma, in which float an innumerable multitude of fine fat-droplets. The latter elements contain the milk-fat, which consists chiefly of neutral fats, stearin, palmitin, and olein, but contains also a small amount of the fats of butyric and caproic acid as well as slight traces of other fatty acid compounds and small amounts of lecithin, cholesterin, and a yellow pigment. Upon standing, a portion of these elements rises to the surface to form the cream. The milk-plasma holds in solution important proteid and carbohydrate compounds as well as the necessary inorganic salts. The proteids are casein, belonging to the group of nucleo-albumins; lactalbumin, which closely resembles the serum-albumin of blood, and lactoglobulin, which is similar to the paraglobulin of blood: the two latter proteids occur in much smaller quantities than the casein.



The chief carbohydrate in milk is the milk-sugar or lactose. Hammarsten<sup>1</sup> has succeeded in isolating from the mammary gland a nucleo-proteid containing a reducing group. He designates this substance as nucleo-glyco-proteid. It seems possible that a compound of this character might serve as the parent substance for both the casein and the lactose of the secretion. The mineral constituents are varied and, considered quantitatively, show an interesting relationship to the mineral composition of the body of the suckling (see p. 357). The fact that the inorganic salts of the milk vary so widely in quantitative composition from those of the blood has been used to show that they are not derived from the blood by the simple mechanical processes of filtration and diffusion, but are secreted by the epithelial cells of the glands. Traces of nitrogenous excreta, such as urea, creatin, and creatinin, are also found in the milk-plasma, together with some lecithin and cholesterin and a small amount of citric acid occurring as citrate of calcium.

**Histological Changes during Secretion.**—The simple fact that substances are found in the milk which do not occur in the blood or lymph is sufficient proof that the epithelial cells are actively concerned in the process of secretion. Histological examination of the gland during lactation confirms

fully this *a priori* deduction, and enables us to understand the probable origin of some of the important constituents.<sup>2</sup> In the resting gland during the period of gestation, or in certain alveoli during lactation, the alveoli are lined by a single layer of flattened or cuboidal cells, which have only a single nucleus, present a granular appearance, and have few or no fat-globules in them (Fig. 66). When such alveoli enter into the active formation of milk the epithelial cells

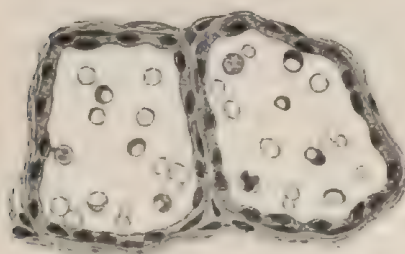


FIG. 66.—Section through the middle of two alveoli of the mammary gland of the dog; condition of rest (after Heidenhain).

increase in height, projecting in toward the lumen, the nuclei divide, and as a

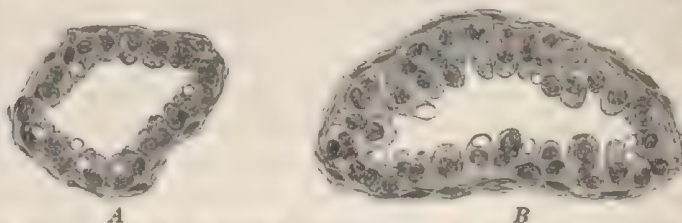


FIG. 67.—Mammary gland of dog, showing the formation of the secretion: A, medium condition of growth of the epithelial cells; B, a later condition (after Heidenhain).

rule (Steinhaus<sup>3</sup>) each cell contains two nuclei (Fig. 67). Fat-droplets develop in the cytoplasm, especially in the free end of the cell, and according to

<sup>1</sup> *Zeitschrift für physiologische Chemie*, 1894, Bd. xix. S. 19.

<sup>2</sup> See Heidenhain: *Hermann's Handbuch der Physiologie*, 1883, Bd. v. S. 381.

<sup>3</sup> *Du Bois-Reymond's Archiv für Physiologie*, 1892, Suppl. Bd., S. 54.

Steinhaus the nucleus nearest the lumen undergoes a fatty metamorphosis. According to the same author the granular material in the cytoplasm also undergoes a visible change; the granules, which in the resting cell are spherical, elongate during the stage of activity to threads that take on a spirochæta-like form. The acme of this phase of development is reached by the solution or disintegration of a portion of the end of the cell, the fragments being discharged into the lumen of the alveolus. The débris of this disintegrated portion of the cell helps to form the secretion; part of it goes into solution to form, probably, the albuminous and carbohydrate constituents, while the fat-droplets are set free to form the milk-fat. Apparently the basal portion of the cell regenerates its cytoplasm and thus continues to form new material for the secretion. In some cases, however, the whole cell seems to undergo dissolution, and its place is taken by a new cell formed by karyokinetic division of one of the neighboring epithelial cells. The origin of the peculiar colostrum corpuscles found in the milk during the first few days of its secretion has been explained differently by different observers. Heidenhain traces them to certain epithelial cells of the alveoli which at this time become rounded, develop numerous fat-droplets, and are finally discharged bodily into the lumen, although he was not able to actually trace the intermediate steps in the process. Steinhaus, on the contrary, thinks that these corpuscles are derived from the wandering cells of the connective tissue (*Mastzellen*) which at the beginning of lactation are very numerous, but seem to undergo fatty degeneration and elimination in the secretion of the newly active gland.

**Control of the Secretion by the Nervous System.**—There are indications that the secretion of the mammary glands is under the control, to some extent at least, of the central nervous system. For instance, in women during the period of lactation cases have been recorded in which the secretion was altered or perhaps entirely suppressed by strong emotions, by an epileptic attack, etc. This indication has not received satisfactory confirmation from the side of experimental physiology. Eckhard<sup>1</sup> found that section of the main nerve-trunk supplying the gland in goats, the external spermatic, caused no difference in the quantity or quality of the secretion. Röhrig<sup>2</sup> obtained more positive results, inasmuch as he found that some of the branches of the external spermatic supply vaso-motor fibres to the blood-vessels of the gland and influence the secretion of milk by controlling the local blood-flow in the gland. Section of the inferior branch of this nerve, for example, gave increased secretion, while stimulation caused diminished secretion, as in the case of the vaso-constrictor fibres to the kidney. These results have not been confirmed by others—in fact, they have been subjected to adverse criticism—and they cannot, therefore, be accepted unhesitatingly.

Mironow<sup>3</sup> reports a number of interesting experiments made upon goats.

<sup>1</sup> See Heidenhain: *Hermann's Handbuch der Physiologie*, Bd. v. Thl. 1. S. 392.

<sup>2</sup> *Vinchow's Archiv für pathologische Anatomie*, etc., 1876, Bd. 67, S. 119.

<sup>3</sup> *Archives des Sciences biologiques*, St. Petersburg, 1894, t. iii. p. 353.



He found that artificial stimulation of sensory nerves causes a diminution in the amount of secretion, thus confirming the opinion based upon observations upon the human being, that in some way the central nervous system exerts an influence on the mammary gland. When the mammary glands are completely isolated from their connections with the central nervous system, stimulation of an afferent nerve no longer influences the secretion. Mironow states also that although section of the external spermatic on one side does not influence the secretion, section of this nerve on both sides is followed by a marked diminution, and the same result is obtained when the gland on one side is completely isolated from all nervous connections. The diminution of the secretion in these cases comes on very slowly, after a number of days, so that the effect cannot be attributed to the removal of definite secretory fibres. Moreover, after apparently complete separation of the gland from all its extrinsic nerves, not only does the secretion, if it was previously present, continue to form although in less quantities, but in operations of this kind upon pregnant animals the glands increase in size during pregnancy and become functional after the act of parturition.

Experiments, therefore, as far as they have been carried, indicate that the gland is under the regulating control of the central nervous system, either through secretory or vaso-motor fibres, but that it is essentially an automatic organ. The bond of connection between it and the uterus seems to be, in part if not entirely, through the blood rather than through the nervous system. It should be added that Arnstein<sup>1</sup> has described a definite connection between the nerve-fibres and the epithelial cells of the gland. If this fact is corroborated it would amount to an histological proof of the existence of special secretory fibres, but the physiological evidence for the same fact is either negative or unsatisfactory.

**Normal Secretion of the Milk.**—As was said in speaking of the histology of the gland, the secreting alveoli are not fully formed until the first pregnancy. During the period of gestation the epithelial cells multiply, the alveoli are formed, and after parturition secretion begins. At first the secretion is not true milk, but a liquid differing in composition and known as the colostrum; this secretion is characterized microscopically by the existence of the colostrum corpuscles, which seem to be wandering cells that have undergone a complete fatty degeneration. After a few days the true milk is formed in the manner already described. According to Röhrig the secretion is continuous, but this statement needs confirmation. As the liquid is formed it accumulates in the enlarged galactophorous ducts, and after the tension has reached a certain point further secretion is apparently inhibited. If the ducts are emptied, by the infant or otherwise, a new secretion begins. The emptying of the ducts, in fact, seems to constitute the normal physiological stimulus to the gland-cells, but how this act affects the secreting cells, whether reflexly or directly, is not known. When the child is weaned the secretion under normal conditions soon ceases and the alveoli undergo retrograde changes, although

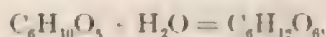
<sup>1</sup> *Anatomischer Anzeiger*, 1895, Bd. x. S. 410.

they do not return completely to the condition they were in before the first pregnancy.

#### INTERNAL SECRETIONS.

According to the definition proposed on p. 211, the term internal secretion is here used to mean a specific substance or substances formed within a glandular organ and given off to the blood or lymph. As was said before, it is difficult to make a distinction between these internal secretions and the waste products of metabolism generally so far as method and place of formation and elimination are concerned. Every active tissue gives off waste products that are borne off in the lymph and blood, but as generally employed the term internal secretion is not meant to include all such products, but only the materials produced in distinctly glandular organs which are more or less specific to those organs, and which are supposed to have a general value to the body as a whole. The idea of an internal secretion seems to have been suggested by Bernard, but was first seriously forced upon the attention of physiologists by Brown-Séquard in the course of some work upon extracts of the testis. Within the last few years the term has been frequently used, especially in connection with the valuable and interesting work done upon the pancreas and the so-called blood-vascular or ductless glands, the thyroids, adrenals, pituitary body, and spleen. In almost all cases our knowledge of the nature and importance of these internal secretions is in a formative stage; the literature, however, of the subject is already very great, and is increasing rapidly, while speculations are numerous, so that constant contact with current literature is necessary to keep pace with the advance in knowledge.

**Liver.**—It has not been customary to speak of the liver as furnishing an internal secretion, but two of the products formed within this organ are so clearly known and their method of production is so typical of what is supposed to be the mechanism of internal secretion, that it is desirable both for the sake of convenience and consistency to include them under this general heading. Glycogen ( $C_6H_{10}O_5$ )<sub>n</sub> is formed within the liver-cells from the sugars and proteids brought to them in the blood of the portal vein, and in many cases the presence of this glycogen can be demonstrated microscopically within the cells. From time to time, however, the glycogen within the cell is converted into dextrose by a process of hydration,



and the sugar so formed is by a secretory process of some kind given off to the blood to serve for the metabolism of the other tissues of the body, especially the muscles. This elimination of its stored glycogen on the part of the liver may be regarded as a case of internal secretion. (For further details concerning glycogen, its properties and functions, see p. 326 and the section on Chemistry.) A second substance which is formed under the influence of the liver-cells and is then eliminated into the blood is urea. Urea constitutes the chief nitrogenous end-product of the metabolism of the proteid tissues; it



is eliminated from the body by the kidneys, but it is known not to be formed in these organs. Modern investigations have seemed to show conclusively that this substance is formed mainly within the liver from some antecedent body (ammonia compound) which arises in the proteid tissues generally, but is not prepared for final elimination until in the liver or elsewhere it is converted into urea. Here again the liver-cells perform a metabolism for the good of the organism as a whole, and the act of passing out the urea into the blood may be regarded as an internal secretion. It is quite possible that in still other ways the liver-cells add to the blood elements of importance to the tissues of the body—as, for example, in the conservation and distribution of the iron of broken-down hæmoglobin (see p. 323), or in the synthetic combination of the products of putrefaction formed in the intestines (indol, skatol, phenol, etc.) with sulphuric acid (see p. 340); but concerning these matters our knowledge is not yet sufficiently definite to make positive statements.

**Pancreas.**—The importance of the external secretion, the pancreatic juice, of the pancreas has long been recognized, but it was not until 1889 that von Mehring<sup>1</sup> and Minkowski proved that it furnishes also an equally important internal secretion. These observers succeeded in extirpating the entire pancreas without causing the immediate death of the animal, and found that in all cases this operation was followed by the appearance of sugar in the urine in considerable quantities. Further observations of their own and other experimenters<sup>2</sup> have corroborated this result and added a number of interesting facts to our knowledge of this side of the activity of the pancreas. It has been shown that when the pancreas is completely removed a condition of glycosuria inevitably follows, even if carbohydrate food is excluded from the diet. Moreover, as in the similar pathological condition of glycosuria or diabetes mellitus in man, there is an increase in the quantity of urine (polyuria) and of urea, and an abnormal thirst and hunger. Acetone also is present in the urine. These symptoms in cases of complete extirpation of the pancreas are followed by emaciation and muscular weakness, which finally end in death in two to four weeks. If the pancreas is incompletely removed, the glycosuria may be serious, or slight and transient, or absent altogether, depending upon the amount of pancreatic tissue left. According to the experiments of von Mehring and Minkowski on dogs, a residue of one-fourth to one-fifth of the gland is sufficient to prevent the appearance of sugar in the urine, although a smaller fragment may suffice apparently if its physiological condition is favorable. The portion of pancreas left in the body may suffice to prevent glycosuria, partly or completely, even though its connection with the duodenum is entirely interrupted, thus indicating that the suppression of the pancreatic juice is not responsible for the glycosuria. The same fact is shown more conclusively by the following experiments: Glycosuria after complete removal of the pancreas from its normal connections may be prevented par-

<sup>1</sup> *Archiv für exper. Pathologie und Pharmacologie*, 1890, Bd. xxvi, S. 371. See also Minkowski, *Ibid.*, 1893, Bd. xxxi, S. 85, for a more complete account.

<sup>2</sup> See Hédon: *Diabète pancréatique*, *Travaux de Physiologie Université de Montpellier*, 1893.

tially or completely by grafting a portion of the pancreas elsewhere in the abdominal cavity or even under the skin. The ducts of the gland may be completely occluded by ligature or by injection of paraffin without causing a condition of permanent glycosuria.

The condition of glycosuria produced by removal of the pancreas is designated frequently as pancreatic diabetes and offers many analogies to the similar pathological condition in man known as diabetes mellitus. The cause of the glycosuria is obscure. It has been shown that in severe cases sugar appears in the urine even when the animal is deprived of food, although the quantity is increased by feeding and especially by carbohydrate food. Examination of the blood shows that the percentage of sugar in it is increased above the normal, from 0.15 per cent. to 0.3 or 0.5 per cent. In the liver, on the contrary, the supply of glycogen disappears. Carbohydrate foods when fed cause no deposition of glycogen in the liver, and apparently escape consumption in the body, being eliminated in the urine. It is said, however, that one form of sugar, levulose, offers an exception to this general rule, since it causes a formation of liver glycogen and seemingly is consumed in the body.

We may believe from these experiments that the pancreas produces a substance of some kind that is given off to the blood or lymph, and is either necessary for the normal consumption of sugar in the body, or else, as is held by some,<sup>1</sup> normally restrains the output of sugar from the liver and other sugar-producing tissues of the body. What this material is and how it acts has not yet been determined satisfactorily. The most plausible theory suggested is that the internal secretion produced contains a special enzyme, glycolytic enzyme (Lépine), whose presence in the blood is necessary for the consumption of the sugar. Such an enzyme may be obtained from blood (p. 354), but it is not proved whether it is a normal constituent or whether it is produced after the blood is shed by the disintegration of some of its corpuscular elements. This theory therefore cannot be considered as more than a possibility. It is interesting and suggestive to state in this connection that post-mortem examination in cases of diabetes mellitus in the human being has shown that this disease is associated in some instances with obvious alterations in the structure of the pancreas.

**The Thyroid Body.**—The thyroids are glandular structures found in all the vertebrates. In the mammalia they lie on either side of the trachea at its junction with the larynx. In man they are united across the front of the trachea by a narrow band or isthmus, and hence are sometimes spoken of as one structure, the thyroid body. In some of the lower mammals (*e. g.* dog) the isthmus is often absent. The thyroids in man are small bodies measuring about 50 millimeters in length by 30 millimeters in width; they have a distinct glandular structure but possess no ducts. Histological examination shows that they are composed of a number of closed vesicles varying in size. Each vesicle is lined by a single layer of cuboidal epithelium, while its interior is filled by a homogeneous glairy liquid, the colloid substance

<sup>1</sup> See Kaufmann. *Archives de Physiologie normale et pathologique*, 1895, p. 210.



which is found also in the tissue between the vesicles lying in the lymph-spaces. This colloid substance is regarded as a secretion from the epithelial cells of the vesicles, and Biondi,<sup>1</sup> Langendorff,<sup>2</sup> and Hürthle<sup>3</sup> claim to have followed the development of the secretion in the epithelial cells by micro-chemical reactions. While the interpretation of the microscopical appearances given by these authors is not the same, they agree in believing that the colloid material is formed within some or all of the epithelial cells, and is eliminated into the lumen with or without a disintegration of the cell-substance. Moreover, Langendorff and Biondi believe that the colloid material is finally discharged into the lymphatics by the rupture of the vesicles. The composition of the colloid is incompletely known.

*Parathyroids.*—The parathyroids are small bodies, two on each side, lying lateral or posterior to the thyroids. One of them may be enclosed within the substance of the thyroid, and is then known as the internal parathyroid, the other being the external parathyroid. They are quite unlike the thyroids in structure, consisting of solid masses or columns of epithelial-like cells which are not arranged to form acinous vesicles. According to Schaper,<sup>4</sup> these bodies are not always paired, but may have a multiple origin extending along the common carotid in the neighborhood of the thyroids.

*Accessory Thyroids.*—In addition to the parathyroids, a variable number of accessory thyroids have been described by different observers, occurring in the neck or even as far down as the heart. These bodies possess the structure of the thyroid, and presumably have the same function. After removal of the thyroids they may suffice to prevent a fatal result.

*Functions of the Thyroids and Parathyroids.*—Very great interest has been excited within recent years with regard to the functions of the thyroids. In 1856 Schiff<sup>5</sup> showed that in dogs complete extirpation of the two thyroids is followed by the death of the animal; and within the last few years similar results have been obtained by numerous observers. Death is preceded by a number of characteristic symptoms, such as muscular tremors, which may pass into spasms and convulsions, cachexia, emaciation, and a more or less marked condition of apathy. The muscular phenomena seem to proceed from the central nervous system, since section of the motor nerves protects the muscles from the irritation. The metabolic changes may also be due primarily to an alteration in the condition of the cord and brain. Similar results have been obtained in cats. Among the herbivorous animals it was at first stated that removal of the thyroids does not cause death; but so far as the rabbit is concerned Gley<sup>6</sup> has shown that if care be taken to remove the parathyroids also, death is as certain and rapid as in the case of the carnivora; a similar result has been obtained upon rats by Christiani. Cases have been reported in which dogs recovered after complete

<sup>1</sup> *Berliner klinische Wochenschrift*, 1888.

<sup>2</sup> *Archiv für Physiologie*, 1889, Suppl. Bd.

<sup>3</sup> *Pflüger's Archiv für die gesammte Physiologie*, 1894, Bd. lvi. S. 1.

<sup>4</sup> *Archiv für mikroskopische Anatomie*, 1895, Bd. xlv. S. 500.

<sup>5</sup> *Archives de Physiologie normale et pathologique*, 1892, p. 135.

thyroidectomy, but these cases are rare and may be explained probably by the presence of accessory thyroids which remain after the operation. It has been observed, too, that the operation is more rapidly and certainly fatal in young animals than in old ones. In the monkey as well as in man the evil results following the removal of the glands develop more slowly than in the lower animals, and give rise to a series of symptoms resembling those of myxœdema in man. Among these symptoms may be mentioned a pronounced anæmia, diminution of muscular strength, failure of the mental powers, abnormal dryness of the skin, loss of hairs, and a peculiar swelling of the subcutaneous connective tissue. Physiologists have shown that in the case of dogs the fatal results following thyroidectomy may be mitigated or entirely obviated by grafting a portion of the gland under the skin or in the peritoneal cavity. If the piece grafted is sufficiently large, the animal recovers apparently completely from the operation. So also in removing the thyroids, if a small portion of the gland, or the parathyroids, be left undisturbed the fatal symptoms do not develop. In human beings suffering from myxœdema as the result of loss of function of the thyroids it has been abundantly shown that injection of thyroid extracts, or feeding the fresh gland, restores the individual to an approximately normal condition. In the earlier experiments on thyroidectomy no distinction was made between the effects of removal of the thyroids and parathyroids, although, as said above, it was noticed that in some animals a fatal result failed to follow the operation unless care was taken to extirpate the parathyroids as well as the thyroids. It was supposed by some that the parathyroids represented an immature or embryonic form of thyroid tissue, and that after the removal of the thyroids the parathyroids took on their function and assumed a thyroid structure. Histological evidence seemed to favor this view, but the latest physiological experiments, on the contrary, have indicated that the parathyroids are not to be regarded as immature structures, but as bodies possessing a definite functional value, distinct from, but not less important than, that of the thyroids themselves. Mousson,<sup>1</sup> whose work has been confirmed in part by others,<sup>2</sup> makes the following distinction in regard to the effect of extirpation of these bodies. Removal of the thyroids and accessory thyroids is followed by a slowly developing general trophic disturbance, a progressive cachexia that produces a condition resembling myxœdema. In young animals the effect is more marked and causes a condition of cretinism. The animals, therefore, may survive complete thyroidectomy, for long periods at least. Removal of all the parathyroids, on the contrary, is followed by acute disturbances and rapid death, the symptoms being the same as those formerly described as resulting from complete thyroidectomy. It would seem from these results that both the thyroids and the parathyroids play an important part in the general metabolism of the body.

<sup>1</sup> *Proceedings of Fourth International Physiological Congress, Cambridge, 1898.*

<sup>2</sup> *Gley: Archiv für die gesammte Physiologie, 1897, Bd. lxxi. S. 308.*



Two views prevail as to the general nature of their function.<sup>1</sup> According to some, the office of these bodies is to remove some toxic substance or substances which normally accumulate in the blood as the result of the body-metabolism. If the thyroids or parathyroids are extirpated, the corresponding substance then increases in quantity and produces the observed symptoms by a process of auto-intoxication. In support of this view there are numerous observations to show that the blood, or urine, or muscle-juice of thyroid-ectomized animals has a toxic effect upon sound animals. These latter results, however, do not appear to be marked or invariable, and in the hands of some experimenters have failed altogether. The second view is that the thyroids and parathyroids secrete each a material, a true internal secretion, which after getting into the blood plays an important and indeed essential part in the metabolic changes of some or all of the organs of the body, but especially the central nervous system. In support of this view we have such facts as these: Injections of properly prepared thyroid extracts have a beneficial and not an injurious influence; there is microscopic evidence to show that the epithelial cells participate actively in the formation of the colloid secretion, and that this secretion eventually reaches the blood by way of the lymph-vessels; the beneficial material in the thyroid extracts may be obtained from the gland by methods which prove that it is a distinct and stable substance formed in the gland, as we might suppose would be the case if it formed part of a definite secretion. This latter fact, indeed, amounts to a proof that the important function of the thyroids is connected with a material secreted within its substance; but it may still be questioned, perhaps, whether this material acts by antagonizing toxic substances produced elsewhere in the body or by directly influencing the body metabolism. For a more specific theory of the functional value of the thyroids proposed by Cyon<sup>2</sup> reference must be made to original sources. Much work has been done to isolate the beneficial material of the thyroid, particularly in relation to the therapeutic use of the gland in myxedema and goitre. The mere fact that feeding the gland acts as well as injecting its extracts shows the resistant nature of the substance, since it is evidently not injured by the digestive secretions. It has been shown also by Baumann<sup>3</sup> that the gland material may be boiled for a long period with 10 per cent. sulphuric acid without destroying the beneficial substance. This observer has succeeded in isolating from the gland a substance to which the name *iodothyrim* is given, which is characterized by containing a relatively large percentage (9.3 per cent. of the dry weight) of iodine, and which preserves in large measure the beneficial influence of thyroid extracts in cases of myxedema and parenchymatous goitre. In the parathyroid tissue the same material is contained in relatively larger quantities. This notable discovery shows that thyroid tissue has the

<sup>1</sup> See Schaefer: "Address on Physiology," annual meeting of the British Medical Association, London, July-August, 1895.

<sup>2</sup> *Archives de Physiologie*, 1898, p. 618.

<sup>3</sup> *Zeitschrift für physiologische Chemie*, 1896, Bd. xxi. S. 319.

power of forming a specific organic compound of iodine, and it is possible that its influence upon body-metabolism may be connected with this fact. Baumann and Roos<sup>1</sup> state that the iodothyrim is contained within the gland mainly in a state of combination with proteid bodies, from which it may be separated by digestion with gastric juice or by boiling with acids. Most of the substance is combined with an albuminous proteid, while a smaller part is united with a globulin-like proteid. There can be little doubt that the authors have succeeded in isolating at least one of the really effective substances of thyroid extracts. If the distinction made between the functions of the thyroids and parathyroids proves to be correct, and if each of these glands exercises its functions by means of an internal secretion, we may hope that future work will be able to isolate the distinctive substance or substances characteristic of each gland.

**Adrenal Bodies.**—The adrenal bodies—or, as they are frequently called in human anatomy, the suprarenal capsules—belong to the group of ductless glands. Their histology as well as their physiology is incompletely known. It was shown first by Brown-Séquard (1856) that removal of these bodies is followed rapidly by death. This result has been confirmed by many experimenters, and so far as the observations go the effect of complete removal is the same in all animals. The fatal effect is more rapid than in the case of removal of the thyroids, death following the operation usually in two to three days, or, according to some accounts, within a few hours. The symptoms preceding death are great prostration, muscular weakness, and marked diminution in vascular tone. These symptoms are said to resemble those occurring in Addison's disease in man, a disease which clinical evidence has shown to be associated with pathological lesions in the suprarenal capsules. It has been expected, therefore, that the results obtained for thyroid treatment of myxœdema might be repeated in cases of Addison's disease by the use of adrenal extracts. These expectations seem to have been realized in part, but complete and satisfactory reports are yet lacking. The physiology of the adrenals has usually been explained upon the auto-intoxication theory. The death that comes after their removal has been accounted for upon the supposition that during life they remove or destroy a toxic substance produced elsewhere in the body, possibly in the muscular system. Oliver<sup>2</sup> and Schaefer, and, about the same time, Cybulski and Szymonowicz,<sup>3</sup> have given reasons for believing that this organ forms a peculiar substance that has a very definite physiological action especially upon the circulatory system. They find that aqueous extracts of the medulla of the gland when injected into the blood of a living animal have a remarkable influence upon the heart and blood-vessels. If the vagi are intact, the adrenal extracts cause a very marked slowing of the heart-beat together with a rise of blood-pressure. When the inhibiting fibres of the vagus are thrown out of action by section or by the use of atropin the heart-

<sup>1</sup> *Zeitschrift für physiologische Chemie*, 1896, Bd. xxi. S. 481.

<sup>2</sup> *Journal of Physiology*, 1895, vol. xviii. p. 230.

<sup>3</sup> *Archiv für die gesamte Physiologie*, 1896, Bd. lxxiv. S. 97.



rate is accelerated, while the blood-pressure is increased sometimes to an extraordinary extent. These facts are obtained with very small doses of the extracts. Schaefer states that as little as  $5\frac{1}{2}$  milligrams of the dried gland may produce a maximal effect upon a dog weighing 10 kilograms. The effects produced by such extracts are quite temporary in character. In the course of a few minutes the blood-pressure returns to normal, as also the heart-beat, showing that the substance has been destroyed in some way in the body, although where or how this destruction occurs is not known. According to Schaefer, the kidneys and the adrenals themselves are not responsible for this prompt elimination or destruction of the injurious substance. The constriction of the blood-vessels seems to be due to a direct effect on the muscles in the walls of the vessels, in part at least, since it is present after destruction of the vaso-motor centre and most or, indeed, all of the spinal cord. Several observers<sup>1</sup> have shown satisfactorily that the material producing this effect is present in perceptible quantities in the blood of the adrenal vein, so that there can be but little doubt that it is a distinct internal secretion of the adrenal. Dreyer has shown, moreover, that the amount of this substance in the adrenal blood is increased, judging from the physiological effects of its injection, by stimulation of the splanchnic nerve. Since this result was obtained independently of the amount of blood-flow through the gland, Dreyer makes the justifiable assumption that the adrenals possess secretory nerve fibres. Abel<sup>2</sup> has succeeded in isolating the substance that produces the effect on blood-pressure and heart-rate, and proposes for it the name epinephrin. He assigns to it the formula  $C_{17}H_{13}NO_3$ , and describes it as a peculiar unstable basic body. Salts of epinephrin were obtained which when injected into the circulation caused the typical effects produced by injection of extracts of the gland. It is possible that the substance in question may be continually secreted under normal conditions by the adrenal bodies and play a very important part with reference to the functional activity of the muscular tissues.

**Pituitary Body.**—This body is usually described as consisting of two parts, a large anterior lobe of distinct glandular structure, and a much smaller posterior lobe, whose structure is not clearly known, although it contains nerve-cells and also apparently some glandular cells. Embryologically the two lobes are entirely distinct. The anterior lobe, which it is preferable to call the hypophysis cerebri, arises from the epithelium of the mouth, while the posterior lobe, or the infundibular body, develops as an outgrowth from the infundibulum of the brain, and in the adult remains connected with this portion of the brain by a long stalk. Howell<sup>3</sup> and others have shown that extracts of the hypophysis when injected intravenously have little or no physiological effect, while extracts of the infundibular body, on the contrary,

<sup>1</sup> *American Journal of Physiology*, 1899, vol. ii. p. 203.

<sup>2</sup> *Zeitschrift für physiologische Chemie*, 1899, Bd. xxviii. S. 318.

<sup>3</sup> *Journal of Experimental Medicine*, 1898, vol. iii. p. 245; also Schaefer and Vincent: *Journal of Physiology*, 1899, vol. xxv. p. 87.

cause a marked rise of blood-pressure and slowing of the heart-beat. These effects resemble in general those obtained from adrenal extracts, but differ in some details. They seem to warrant the conclusion that the infundibular body is not a mere rudimentary organ, as has been generally assumed, but produces a peculiar substance, an internal secretion, that may have a distinct physiological value. A number of observers, especially Vassale and Sacchi, have succeeded in removing the entire pituitary body. They report that the operation results eventually in the death of the animal with a certain group of symptoms, such as muscular tremors and spasms, apathy and dyspnoea, that resemble the results of thyroidectomy. It has been suggested therefore that the pituitary body may be related in function to the thyroids and may be able to assume vicariously the functions of the latter after thyroidectomy. There is no satisfactory evidence, however, in support of this view. On the pathological side it has been shown that usually lesions of the pituitary body, particularly of the hypophysis, are associated with a peculiar disease known as acromegaly, the most prominent symptom of which is a marked hypertrophy of the bones of the extremities and of the face. The conclusion sometimes drawn from this fact that acromegaly is caused by a disturbance of the functions of the pituitary body is, however, very uncertain, and is not supported by any definite clinical or experimental facts.

**Testis and Ovary.**—Some of the earliest work upon the effect of the internal secretions of the glands was done upon the reproductive glands, especially the testis, by Brown-Séquard.<sup>1</sup> According to this observer, extracts of the fresh testis when injected under the skin or into the blood may have a remarkable influence upon the nervous system. The general mental and physical vigor, and especially the activity of the spinal centres, are greatly improved, not only in cases of general prostration and neurasthenia, but also in the case of the aged. Brown-Séquard maintained that this general dynamogenic effect is due to some unknown substance formed in the testis and subsequently passed into the blood, although he admitted that some of the same substance may be found in the external secretion of the testis—*i. e.*, the spermatie liquid. More recently Poehl<sup>2</sup> asserts that he has prepared a substance, spermin, to which he gives the formula  $C_5H_{14}N_2$ , which has a very beneficial effect upon the metabolism of the body. He believes that this spermin is the substance that gives to the testicular extracts prepared by Brown-Séquard their stimulating effect. He claims for this substance an extraordinary action as a physiological tonic. The precise scientific value of the results of experiments with the testicular extracts cannot be estimated at present, in spite of the large literature upon the subject; we must wait for more detailed and exact experiments, which doubtless will soon be made. Zoth<sup>3</sup> and also Pregel<sup>4</sup> seem to have obtained exact objective proof, by means

<sup>1</sup> *Archives de Physiologie normale et pathologique*, 1889-92.

<sup>2</sup> *Zeitschrift für klinische Medizin*, 1894, Bd. xxvi, S. 133.

<sup>3</sup> *Pflüger's Archiv für die gesammte Physiologie*, 1896, Bd. lxii, S. 335, also 1897, Bd. lxix, S. 386.

<sup>4</sup> *Ibid.*, S. 379.



of ergographic records, of the stimulating action of the testicular extracts upon the neuro-muscular apparatus in man. They find that injections of the testicular extracts cause not only a diminution in the muscular and nervous fatigue resulting from muscular work, but also lessen the subjective fatigue sensations. The fact that the internal secretion of the testis, if it exists at all, is not absolutely essential to the life of the body as a whole, as in the case of the thyroids, adrenals, and pancreas, naturally makes the satisfactory determination of its existence and action a more difficult task.

Similar ideas in general prevail as to the possibility of the ovaries furnishing an internal secretion that plays an important part in general nutrition. In gynecological practice it has been observed that complete ovariectomy with its resulting premature menopause is often followed by distressing symptoms, mental and physical. In such cases many observers have reported that these symptoms may be alleviated by the use of ovarian extracts. So also in the natural, as well as in the premature menopause following operations, it is a frequent, though not invariable, result for the individual to gain noticeably in weight. The probability of an effect of the ovaries on general nutrition is indicated also by the interesting fact that in cases of osteomalacia, a disease characterized by softening of the bones, removal of the ovaries may exert a very favorable influence upon the course of the disease. These indications have found some experimental verification recently in a research by Loewy and Richter<sup>1</sup> made upon dogs. These observers found that complete removal of the ovaries, although at first apparently without effect, resulted in the course of two to three months in a marked diminution in the consumption of oxygen by the animal, measured per kilo. of body-weight. If now the animal in this condition was given ovarian extracts (oöphorin tablets) the amount of oxygen consumed was not only brought to its former normal, but considerably increased beyond it. A similar result was obtained when the extracts were used upon castrated males. The authors believe that their experiments show that the ovaries form a specific substance which is capable of increasing the oxidation of the body.

**Kidney.**—Tigerstedt and Bergman<sup>2</sup> state that a substance may be extracted from the kidneys of rabbits which when injected into the body of a living animal causes a rise of blood-pressure. They get the same effect from the blood of the renal vein. They conclude, therefore, that a substance, for which they suggest the name "rennin," is normally secreted by the kidney into the renal blood, and that this substance causes a vaso-constriction.

<sup>1</sup> *Archiv für Physiologie*, 1899, Suppl. Bd. S. 174.

<sup>2</sup> *Skandinavische Archiv für Physiologie*, 1898, Bd. viii. S. 223; see also Bradford: *Proceedings of the Royal Society*, 1892.

## V. CHEMISTRY OF DIGESTION AND NUTRITION.

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### A. DEFINITION AND COMPOSITION OF FOODS; NATURE OF ENZYMES.

SPEAKING broadly, what we eat and drink for the purpose of nourishing the body constitutes our food. A person in adult life who has reached his maximum growth, and whose weight remains practically constant from year to year, must eat and digest a certain average quantity of food daily to keep himself in a condition of health and to prevent loss of weight. In such a case we may say that the food is utilized to repair the wastes of the body—that is, the destruction of body-material which goes on at all times, even during sleep, but which is increased by the physical and psychical activities of the waking hours—and in addition it serves as the source of heat, mechanical work, and other forms of energy liberated in the body. In a person who is growing—one who is, as we say, laying on flesh or increasing in stature—a certain portion of the food is used to furnish the energy and to cover the wastes of the body, while a part is converted into the new tissues formed during growth. The material that we eat or drink as food is for the most part in an insoluble form, or has a composition differing very widely from that of the tissues which it is intended to form or to repair. The object of the processes of digestion carried on in the alimentary tract is to change this food so that it may be absorbed into the blood, and at the same time so to alter its composition that it can be utilized by the tissues of the body. For we shall find, later on, that certain foods—eggs, for example—which are very nutritious when taken into the alimentary canal and digested cannot be used at all by the tissues if injected at once, unchanged, into the blood. The food of mankind is most varied in character. At different times of the year and in different parts of the world the diet is changed to suit the necessities of the environment. When, however, we come to analyze the various animal and vegetable foods made use of by mankind it is found that they are all composed of one or more of five or six different classes of substances to which the name *food-stuffs* or alimentary principles has been given. To ascertain the nutritive value of any food, it must be analyzed and the percentage amounts of the different food-stuffs contained in it must be determined. The classification of food-stuffs usually given is as follows:



Food-stuffs.	{	Water;
		Inorganic salts;
		Proteids (or proteid-containing bodies);
		Albuminoids (a group of bodies resembling proteids, but having in some respects a different nutritive value);
		Carbohydrates;
		Fats.

The main facts with regard to the specific nutritive value of each of these substances will be given later on, after the processes of digestion have been described. A few general remarks, however, at this place will serve to give the proper standpoint from which to begin the study of the chemistry of digestion and nutrition.

*Water and Salts.*—Water and salts we do not commonly consider as foods, but the results of scientific investigation, as well as the experience of life, show that these substances are absolutely necessary to the body. The tissues must maintain a certain composition in water and salts in order to function normally, and, since there is a continual loss of these substances in the various excreta, they must continually be replaced in some way in the food. It is to be borne in mind in this connection that water and salts constitute a part of all our solid foods, so that the body gets a partial supply at least of these substances in everything we eat.

*Proteids.*—The composition and different classes of proteids are described from a chemical standpoint in the section on The Chemistry of the Body. Different varieties of proteids are found in animal as well as in vegetable foods. The chemical composition in all cases, however, is approximately the same. Physiologically, they are supposed to have equal nutritive values outside of differences in digestibility, a detail that will be given later. The essential use of the proteids to the body is that they supply the material from which the new proteid tissue is made or the old proteid tissue is repaired, although, as we shall find when we come to discuss the subject more thoroughly (p. 345), proteids are also extremely valuable as sources of energy to the body. Inasmuch as the most important constituent of living matter is the proteid part of its molecule, it will be seen at once that proteid food is an absolute necessity. Proteids contain nitrogen, and they are frequently spoken of as the *nitrogenous* foods; carbohydrates and fats, on the contrary, do not contain nitrogen. It follows immediately from this fact that fats and carbohydrates alone could not suffice to make new protoplasm. If our diet contained no proteids, the tissues of the body would gradually waste away and death from starvation would result. All the food-stuffs are necessary in one way or another to the preservation of perfect health, but proteids, together with a certain proportion of water and inorganic salts, are absolutely necessary for the bare maintenance of animal life—that is, for the formation and preservation of living protoplasm. Whatever else is contained in our food, proteid of some kind must form a part of our diet. The use of

the other food-stuffs is, as we shall see, more or less accessory. It may be worth while to recall here the familiar fact that in respect to the nutritive importance of proteids there is a wide difference between animal and vegetable life. What is said above applies, of course, only to animals. Plants can, and for the most part do, build up their living protoplasm upon diets containing no proteid. With some exceptions that need not be mentioned here, the food-stuffs of the great group of chlorophyll-containing plants, outside of oxygen, consist of water,  $\text{CO}_2$ , and salts, the nitrogen being found in the last-mentioned constituent.

*Albuminoids.*—Gelatin, such as is found in soups or is used in the form of table-gelatin, is a familiar example of the albuminoids. They are not found to any important extent in our raw foods, and they do not therefore usually appear in the analyses given of the composition of foods. An examination of the composition and properties of these bodies (see section on The Chemistry of the Body) shows that they resemble closely the proteids. Unlike the fats and carbohydrates, they contain nitrogen, and they are evidently of complex structure. Nevertheless, they cannot be used in place of proteids to build protoplasm. They are important foods without doubt, but their value is similar in a general way to that of the non-nitrogenous foods, fats and carbohydrates, rather than to the so-called "nitrogenous foods," the proteids.

*Carbohydrates.*—We include among carbohydrates the starches, sugars, gums, and the like (see Chemical section); they contain no nitrogen. Their physiological value lies in the fact that they are destroyed in the body and a certain amount of energy is thereby liberated. The energy of muscular work and of the heat of the body comes largely from the destruction or oxidation of carbohydrates. Inasmuch as we are continually giving off energy from the body, chiefly in the form of muscular work and heat, it follows that material for the production of this energy must be taken in the food. Carbohydrates form perhaps the easiest and cheapest source of this energy. They constitute the bulk of our ordinary diet.

*Fats.*—In the group of fats we include not only what is ordinarily understood by the term, but also the oils, animal and vegetable, that form such a common part of our food. Fats contain no nitrogen (see Chemical section). Their use in the body is substantially the same as that of the carbohydrates. Weight for weight, they are more valuable than the carbohydrates as sources of energy, but the latter are cheaper, more completely digested when fed in quantity, and more easily destroyed in the body. For these reasons we find that under most conditions fats are a subsidiary article of food as compared with the carbohydrates. From the standpoint of the physiologist, fats are of special interest because the animal body stores up its reserve of food material mainly in that form. The history of the origin of the fats of the body is one of the most interesting parts of the subject of nutrition, and it will be discussed at some length in its proper place.

As has been said, our ordinary foods are mixtures of some or all of the food-stuffs, together with such things as flavors or condiments, whose nutritive



value is of a special character. Careful analyses have been made of the different articles of food, mostly of the raw or uncooked foods. As might be expected, the analyses on record differ more or less in the percentages assigned to the various constituents, but almost any of the tables published give a just idea of the fundamental nutritive value of the common foods. For details of separate analyses reference may be made to some of the larger works upon the composition of foods.<sup>1</sup> The subjoined table is one compiled by Munk from the analyses given by König:

Composition of Foods.

In 100 parts.	Water.	Proteid.	Fat.	Carbohydrate.		Ash.
				Digestible.	Cellulose.	
Meat . . . . .	76.7	20.8	1.5	0.3	. . .	1.3
Eggs . . . . .	73.7	12.6	12.1	. . .	. . .	1.1
Cheese . . . . .	36-60	25-33	7-30	3-7	. . .	3-4
Cow's milk . . . . .	87.7	3.4	3.2	4.8	. . .	0.7
Human milk . . . . .	89.7	2.0	3.1	5.0	. . .	0.2
Wheat flour . . . . .	13.3	10.2	0.9	74.8	0.3	0.5
Wheat bread . . . . .	35.6	7.1	0.2	55.5	0.3	1.1
Rye flour . . . . .	13.7	11.5	2.1	69.7	1.6	1.4
Rye bread . . . . .	42.3	6.1	0.4	49.2	0.5	1.5
Rice . . . . .	13.1	7.0	0.9	77.4	0.6	1.0
Corn . . . . .	13.1	9.9	4.6	68.4	2.5	1.5
Macaroni . . . . .	10.1	9.0	0.3	79.0	0.3	0.5
Peas, beans, lentils . . . . .	12-15	23-26	1½-2	49-54	4-7	2-3
Potatoes . . . . .	75.5	2.0	0.2	20.6	0.7	1.0
Carrots . . . . .	87.1	1.0	0.2	9.3	1.4	0.9
Cabbages . . . . .	90	2-3	0.5	4-6	1-2	1.3
Mushrooms . . . . .	73-91	4-8	0.5	3-12	1-5	1.2
Fruit . . . . .	84	0.5	. . .	10	4	0.5

An examination of this table will show that the animal foods, particularly the meats, are characterized by their small percentage in carbohydrate and by a relatively large amount of proteid or of proteid and fat. With regard to the last two food-stuffs, meats differ very much among themselves. Some idea of the limits of variation may be obtained from the following table, taken chiefly from König's analyses:

	Water.	Proteid.	Fat.	Carbohydrate.	Ash.
Beef, moderately fat . . . . .	73.03	20.96	5.41	0.46	1.14
Veal, fat . . . . .	72.31	18.88	7.41	0.07	1.33
Mutton, moderately fat . . . . .	75.99	17.11	5.77	. . .	1.33
Pork, lean . . . . .	72.57	20.05	6.81	. . .	1.10
Ham, salted . . . . .	62.58	22.32	8.68	. . .	6.42
Pork (bacon), very fat <sup>2</sup> . . . . .	10.00	3.00	80.50	. . .	6.5
Mackerel <sup>3</sup> . . . . .	71.6	18.8	8.2	. . .	1.4

The vegetable foods are distinguished, as a rule, by their large percentage in carbohydrates and the relatively small amounts of proteids and fats, as seen, for example, in the composition of rice, corn, wheat, and potatoes. Neverthe-

<sup>1</sup> König, *Die Menschlichen Nahrungs und Genussmittel*, 3d ed., 1889; Parke's *Manual of Practical Hygiene*, section on Food.

<sup>2</sup> Atwater: *The Chemistry of Foods and Nutrition*, 1887.

less, it will be noticed that the proportion of proteid in some of the vegetables is not at all insignificant. They are characterized by their excess in carbohydrates rather than by a deficiency in proteids. The composition of peas and other leguminous foods is remarkable for the large percentage of proteid, which exceeds that found in meats. Analyses such as are given here are indispensable in determining the true nutritive value of foods. Nevertheless, it must be borne in mind that the chemical composition of a food is not alone sufficient to determine its precise value in nutrition. It is obviously true that it is not what we eat, but what we digest and absorb, that is nutritious to the body, so that, in addition to determining the proportion of food-stuffs in any given food, it is necessary to determine to what extent the several constituents are digested. This factor can be obtained only by actual experiments. It may be said here, however, that in general the proteids of animal foods are more completely digested than are those of vegetables, and with them, therefore, chemical analysis comes nearer to expressing directly the nutritive value.

The physiology of digestion consists chiefly in the study of the chemical changes that the food undergoes during its passage through the alimentary canal. It happens that these chemical changes are of a peculiar character. The peculiarity is due to the fact that the changes of digestion are effected through the agency of a group of bodies known as *enzymes*, or unorganized ferments, whose chemical action is more obscure than that of the ordinary reagents with which we have to deal. It will save useless repetition to give here certain general facts that are known with reference to these bodies, reserving for future treatment the details of the action of the specific enzymes found in the different digestive secretions.

**Enzymes.**—Enzymes, or unorganized ferments, or unformed ferments, is the name given to a group of bodies produced in animals and plants, but not themselves endowed with the structure of living matter. The term *unorganized* or *unformed* ferment was formerly used to emphasize the distinction between these bodies and living ferments, such as the yeast-plant or the bacteria. "Enzyme," however, is a better name, and is coming into general use. Enzymes are to be regarded as dead matter, although produced in living protoplasm. Chemically, they are defined as complex organic compounds containing nitrogen. Their exact composition is unknown, as it has not been found possible heretofore to obtain them in pure enough condition for analysis. Although several elementary analyses are recorded, they cannot be considered reliable. It is not known whether or not the enzymes belong to the group of proteids. Solutions of most of the enzymes give some or all of the general reactions for proteids, but there is always an uncertainty as to the purity of the solutions. With reference to the fibrin ferment of blood, one of the enzymes, observations have recently been made which seem to show that it belongs to the group of combined proteids, nucleo-albumins (for details see the section on Blood). But even should this be true, we are not justified in making any general application of this fact to the whole group.



*Classification of Enzymes.*—Enzymes are classified according to the kind of reaction they produce—namely:

1. *Proteolytic enzymes*, or those acting upon proteids, converting them to a soluble modification, peptone or proteose. As examples of this group we have in the animal body *pepsin* of the gastric juice and *trypsin* of the pancreatic juice. In plants a similar enzyme is found in the pineapple family (bromelin) and in the papaw (papain).

2. *Amylolytic enzymes*, or those acting upon the starches, converting them to a soluble form, sugar, or sugar and dextrin. As examples of this group we have in the animal body *ptyalin*, found in saliva, *amyllopsin*, found in pancreatic juice, and in the liver an enzyme capable of converting glycogen to sugar. In the plants the best-known example is *diastase*, found in germinating seeds. This particular enzyme has been known for a long time from the use made of it in the manufacture of beer. In fact, the name "diastase" is frequently used in a generic sense, "the diastatic enzymes," to characterize the entire group of starch-destroying ferments.

3. *Fat-splitting enzymes*, or those acting upon the neutral fats, breaking them up into glycerin and the corresponding fatty acid. The best-known example in the animal body is found in the pancreatic secretion; it is known usually as *steapsin*, although it has been given several names. Similar enzymes are known to occur in a number of seeds.

4. *Sugar-splitting enzymes*, or those having the property of converting the double into the single sugars—the di-saccharides, such as *cane-sugar* and *maltose*, into the mono-saccharides, such as *dextrose* and *levulose*. Two enzymes of this character are found in the small intestine of the animal body, one acting upon cane-sugar and one on maltose. The one acting on cane-sugar is known as invertine or invertase, while that acting on maltose is designated as maltase.

5. *Coagulating enzymes*, or those acting upon soluble proteids, precipitating them in an insoluble form. As examples of this class we have fibrin ferment (*thrombin*), formed in shed blood, and *rennin*, the milk-curdling ferment of the gastric juice. An enzyme similar to rennin has been found in pineapple-juice.

These five classes comprise the chief groups of enzymes that are known to occur in the animal body. One or more examples of each group take part in the digestion of food at some time during its passage through the alimentary canal. From time to time other enzymes have been recognized in the liquids or tissues of the body.<sup>1</sup> Thus in shed blood and indeed in other tissues an enzyme (glycolytic enzyme) that is capable of destroying sugar seems to be present. When sugar is added to shed blood it disappears as such, although the products formed have not been recognized. Similarly from many tissues of the body oxidizing enzymes have been extracted that are capable of causing energetic oxidation of organic bodies; for instance, they can convert salicylaldehyde to salicylic acid. It is possible that these oxidizing enzymes,

<sup>1</sup> For a recent summary of facts and literature upon enzymes see Green: *The Soluble Ferments and Fermentation*, 1897.

or *oxidases*, form a group that plays an important part in the functional metabolism of the tissues, but at present our knowledge of their existence and functional value in the living organism is very uncertain.

A great number of general reactions have been discovered, applicable, with an exception here and there, to the whole group of enzymes. Among these reactions the following are the most useful or significant:

1. *Solubility*.—The enzymes are soluble in water. They are also soluble in glycerin, this being the most generally useful solvent for obtaining extracts of the enzymes from the organs in which they are formed.

2. *Effect of Temperature*.—In a moist condition they are destroyed by temperatures below the boiling-point;  $60^{\circ}$  to  $80^{\circ}$  C. are the limits actually observed. Very low temperatures retard or even suspend entirely ( $0^{\circ}$  C.) their action, without, however, destroying the enzyme. For each enzyme there is a temperature at which its action is greatest.

3. *Incompleteness of Action*.—With the exception perhaps of the coagulating enzymes, they are characterized by the fact that in any given solution they never completely destroy the substance upon which they act. It seems that the products of their activity, as they accumulate, finally prevent the enzymes from acting further; when these products are removed the action of the enzyme begins again. The most familiar example of this very striking peculiarity is found in the action of pepsin on proteids. The products of digestion in this case are peptones and proteoses, and when they have reached a certain concentration they prevent any further proteolysis on the part of the pepsin.

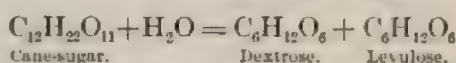
4. *Relation of the Amount of Enzyme to the Effect it Produces*.—With most substances the extent of the chemical change produced is proportional to the amount of the substance entering into the reaction. With the enzymes this is not so. Except for very small quantities, it may be said that the amount of change caused is independent of the amount of enzyme present, or, to state the matter more accurately, "with increasing amounts of enzymes the extent of action also increases, reaching a maximum with a certain percentage of enzyme; increase of enzyme beyond this has no effect."<sup>1</sup> This fact was formerly interpreted to mean that the enzyme is not used up—that is, not permanently altered—by the reaction that it causes. This belief, indeed, must be true substantially, but it has been found practically that a given solution of enzyme cannot be used over and over again indefinitely. It is generally believed now that, although an enzyme causes an amount of change in the substance it acts upon altogether out of proportion to the amount of its own substance, nevertheless it is eventually destroyed; its action is not unlimited. Whether this using up of the enzyme is a necessary result of its activity, or is, as it were, an accidental effect from spontaneous changes in its own molecule, remains undetermined.

**Theories of the Manner of Action of the Enzymes.**—It is now believed that the action of many of the body enzymes, especially the digestive enzymes, is that of hydrating agents; they produce their effect by what is

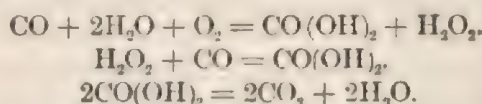
<sup>1</sup>Taunmann: *Zeitschrift für physiologische Chemie*, 1892, Bd. xvi. S. 271.



known as *hydrolysis*; that is, they cause the molecules of the substance upon which they act to take up one or more molecules of water; the resulting molecule then splits or is dissociated, with the formation of two or more simpler bodies. This is one of the most significant facts in connection with the action of the enzymes; it is well illustrated by the action of invertin on cane-sugar, as follows:



In what way enzymes cause the substances they act upon to take up water is unknown. The fact that they are not themselves used up in the reaction proportionally to the change they cause formerly influenced physiologists and chemists to explain their effect as due to *catalysis*, or contact action. In its original sense this designation meant that the molecules of enzyme act by their mere presence or contiguity, but it need scarcely be said that a statement of this kind does not amount to an explanation of their manner of action; to say they "act by catalysis" means nothing in itself. Efforts to explain their action have resulted in a number of hypotheses, a detailed account of which would hardly be appropriate here. It may be mentioned that two ideas have found most general acceptance: one, that the enzyme acts by virtue of some peculiar physical property, such as the physical state of its molecules, or by setting up vibrations in the molecules of the substance acted upon; the other idea is that the enzyme enters into a definite chemical reaction, in which, however, it plays the part of a carrier or go-between, so that, although the enzyme is directly concerned in producing a chemical change, the final outcome is that it remains in its original condition. A number of chemical reactions of this general character are known, in which some one substance passes through a cycle of changes, aiding in the production of new compounds, but itself returning always to its first condition; for example, the part taken by  $\text{H}_2\text{SO}_4$  in the manufacture of ether from alcohol, or the successive changes of hæmoglobin to oxyhæmoglobin and back again to hæmoglobin after giving up its oxygen to the tissues. Perhaps the most suggestive reaction of this character is the one quoted by Chittenden<sup>1</sup> to illustrate this very hypothesis as to the manner of action of enzymes, as follows: Oxygen and carbon monoxide gas, if perfectly dry, will not react upon the passage of an electric spark. If, however, a little aqueous vapor is present, they may be made to unite readily, with the formation of  $\text{CO}_2$ . The water in this case, without doubt, enters into the reaction, but in the end it is re-formed, and the final result is as though the water had not directly participated in the process. The reactions supposed to take place are explained by the following equations:



<sup>1</sup> Cartwright Lectures, *Medical Record*, New York, April 7, 1894.

## B. SALIVARY DIGESTION.

The first of the digestive secretions with which the food comes in contact is *saliva*. This liquid is a mixed secretion from the six large salivary glands (parotids, submaxillaries, and sublinguals) and the smaller mucous and serous glands that open into the mouth. The physiological anatomy of these glands and the mechanism by which the secretions are produced and regulated will be found described fully in the section on Secretion; we are concerned here only with the composition of the secretion after it is formed, and with its action upon foods.

**Properties and Composition of the Mixed Saliva.**—Filtered saliva is a clear, viscid, transparent liquid. As obtained usually from the mouth, it is more or less turbid, owing to the presence in it, in suspension, of particles of food or of detached cells from the epithelium of the mouth. A somewhat characteristic cell contained in it in small numbers is the so-called "salivary corpuscle." These bodies are probably leucocytes, altered in structure, that have escaped into the secretion. So far as is known, they have no physiological value. The specific gravity of the mixed secretion is on an average 1003, and its reaction is normally alkaline. The total amount of secretion during twenty-four hours varies naturally with the individual and the conditions of life; the estimates made vary from 300 to 1500 grams. Chemically, in addition to the water, the saliva contains mucin, ptyalin, albumin, and inorganic salts. The proportions of these constituents are given in the following analysis (Hammerbacher):

	In 1000 parts.
Water . . . . .	994.203
Solids:	
{ Mucin (and epithelial cells) . . . . .	2.202
{ Ptyalin and albumin . . . . .	1.390
{ Inorganic salts . . . . .	2.205
Potassium sulphocyanide . . . . .	0.041
	5.797

The inorganic salts, in addition to the sulphocyanide, which occurs only in traces, consist of the chlorides of potassium and sodium, the sulphate of potassium, and the phosphates of potassium, sodium, calcium, and magnesium; the earthy phosphates form about 9.6 per cent. of the total ash. *Mucin* is an important constituent of saliva; it gives to the secretion its ropy, viscid character, which is of so much value in the mechanical function it fulfils in swallowing. This substance is formed in the salivary glands. Its formation in the protoplasm of the cells may be followed microscopically (see the section on Secretion). Chemically, it is now known to be a combination of a proteid with a carbohydrate group (see section on The Chemistry of the Body). So far as known, mucin has no function other than its mechanical use. The presence of potassium sulphocyanide (KCN) among the salts of saliva has always been considered interesting, since, although it occurs normally in urine as well as in saliva, it is not a salt found commonly in the secretions of the body, and its occurrence in saliva seemed to indicate some special activity on the part of the salivary gland, the possible value of which has been a subject of specula-

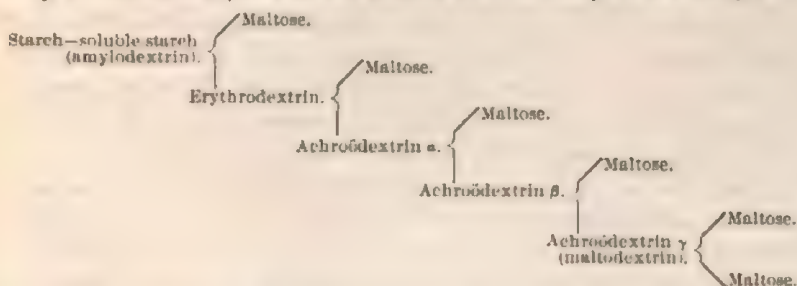


tion. In the saliva, however, the sulphocyanide is found in such minute traces and its presence is so inconstant that no special functional importance can be attributed to it. It is supposed to be derived from the decomposition of proteids, and it represents, therefore, one of the end-products of proteid metabolism. Potassium sulphocyanide may be detected in saliva by adding to the latter a dilute acidulated solution of ferric chloride, a reddish color being produced.

**Ptyalin and its Action.**—From a physiological standpoint the most important constituent of saliva is *ptyalin*. It is an unorganized ferment or enzyme belonging to the amylolytic or diastatic group (p. 280) and possessing the general properties of enzymes already enumerated. It is found in human saliva and in that of many of the lower animals—for example, the pig and the herbivora—but it is said to be absent in the carnivora. Ptyalin has not been isolated in a sufficiently pure condition for satisfactory analysis, so that its chemical nature is undetermined; we depend for its detection upon its specific action—that is, its effect upon starch. Speaking roughly, we say that ptyalin converts starch into sugar, but when we come to consider the details of its action we find that it is complicated and that it consists in a series of hydrolytic splittings of the starch molecule, the exact products of the reaction depending upon the stage at which the action is interrupted. To demonstrate the action of ptyalin on starch it is only necessary to make a suitable starch paste by boiling some powdered starch in water, and then to add a little fresh saliva. If the mixture is kept at a proper temperature ( $30^{\circ}$  to  $40^{\circ}$  C.), the presence of sugar may be detected within a few minutes. The sugar that is formed was for a time supposed to be ordinary grape-sugar (dextrose,  $C_6H_{12}O_6$ ), but later experiments have shown conclusively that it is maltose ( $C_{12}H_{22}O_{11} \cdot H_2O$ ), a form of sugar more closely related in formula to cane-sugar (see Chemical section). In experiments of the kind just described two facts may easily be noticed: first, that the conversion of starch to sugar is not direct, but occurs through a number of intermediate stages; second, that the starch is not entirely converted to sugar under the conditions of such experiments—namely, when the digestion is carried on in a vessel, digestion *in vitro*. The second fact is an illustration of the incompleteness of action of the enzymes, a general property that has already been noticed. We may suppose, in this as in other cases, that the products of digestion, as they accumulate in the vessel, tend to retard and finally to suspend the amylolytic action of the ptyalin. In normal digestion, however, it is usually the case that the products of digestion, as they are formed, are removed by absorption, and if the above explanation of the cause of the incompleteness of action is correct, then under normal conditions we should expect a complete conversion of starch to sugar. Lea<sup>1</sup> states that if the products of ptyalin action are partially removed by dialysis during digestion *in vitro*, a much larger percentage of maltose is formed. His experiments would seem to indicate that in the body the action of the amylolytic ferments

<sup>1</sup> *Journal of Physiology*, 1890, vol. xi. p. 227.

may be complete, and that the final product of their action may be maltose alone. It will be found that this statement applies practically not to the ptyalin, but to the similar amylolytic enzyme in the pancreatic secretion, owing to the fact that, normally, food is held in the mouth for a short time only, and that ptyalin digestion is soon interrupted after the food reaches the stomach. With reference to the intermediate stages or products in the conversion of starch to sugar it is difficult to give a perfectly clear account. It was formerly thought that the starch was first converted to dextrin, and this in turn was converted to sugar. It is now believed that the starch molecule, which is quite complex, consisting of some multiple of  $C_6H_{10}O_5$ —possibly  $(C_6H_{10}O_5)_{20}$ —first takes up water, thereby becoming soluble (soluble starch, amylo-dextrin), and then splits, with the formation of dextrin and maltose, and that the dextrin again undergoes the same hydrolytic process, with the formation of a second dextrin and more maltose; this process may continue under favorable conditions until only maltose is present. The difficulty at present is in isolating the different forms of dextrin that are produced. It is usually said that at least two forms occur, one of which gives a red color with iodine, and is therefore known as *erythro-dextrin*, while the other gives no color reaction with iodine, and is termed *achroö-dextrin*. It is pretty certain, however, that there are several forms of achroö-dextrin, and, according to some observers, erythro-dextrin also is really a mixture of dextrans with maltose in varying proportions. In accordance with the general outline of the process given above, Neumeister<sup>1</sup> proposes the following schema, which is useful because it gives a clear representation of one theory, but which must not be considered as satisfactorily demonstrated (see also the section on Chemistry of the Body).



This schema represents the possibility of an ultimate conversion of all the starch into maltose, and it shows at the same time that maltose may be present very early in the reaction, and that it may occur together with one or more dextrans, according to the stage of the digestion. It should be said in conclusion that this description of the manner of action of the ptyalin is supposed to apply equally well to the amylolytic enzyme of the pancreatic secretion, the two being, so far as known, identical in their properties. From the standpoint of relative physiological importance the description of the details of amylolytic digestion should have been left until the functions of the pancreatic juice were considered. It is introduced here because, in the natural order

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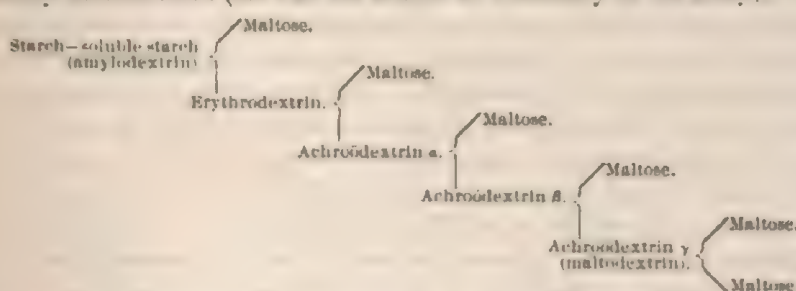


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<sup>1</sup> *Lehrbuch der physiologischen Chemie*, 1893, p. 232.



of treatment, ptyalin is the first of this group of ferments to be encountered. It is interesting also to remember in this connection that starch can be converted into sugar by a process of hydrolytic cleavage by boiling with dilute mineral acids. Although the general action of dilute acids and of amylolytic enzymes is similar, the two processes are not identical, since in the first process dextrose is the sugar formed, while in the second it is maltose. Moreover, variations in temperature affect the two reactions differently.

**Conditions Influencing the Action of Ptyalin.**—*Temperature.*—As in the case of the other enzymes, ptyalin is very susceptible to changes of temperature. At  $0^{\circ}$  C. its activity is said to be suspended entirely. The intensity of its action increases with increase of temperature from this point, and reaches its maximum at about  $40^{\circ}$  C. If the temperature is raised much beyond this point, the action of the ptyalin decreases, and at from  $65^{\circ}$  to  $70^{\circ}$  C. the enzyme is destroyed. In these latter points ptyalin differs from diastase, the enzyme of malt. Diastase shows a maximum action at  $50^{\circ}$  C. and is destroyed at  $80^{\circ}$  C.

*Effect of Reaction.*—The normal reaction of saliva is slightly alkaline. Chittenden has shown, however, that ptyalin acts as well, or even better, in a perfectly neutral medium. A strong alkaline reaction retards or prevents its action. The most marked influence is exerted by acids. Free hydrochloric acid to the extent of only 0.003 per cent. (Chittenden) is sufficient to practically stop the amylolytic action of enzyme, and a slight increase in acidity not only stops the action, but also destroys the enzyme. The latter fact is of practical importance because it indicates that the action of ptyalin on starch must be suspended after the food reaches the stomach.

*Condition of the Starch.*—It is a well-known fact that the conversion of starch to sugar by enzymes takes place much more rapidly with cooked starch—for example, starch paste. In the latter condition sugar begins to appear in a few minutes (one to four), provided a good enzyme solution is used. With starch in a raw condition, on the contrary, it may be many minutes, or even several hours, before sugar can be detected. The longer time required for raw starch is partly explained by the well-known fact that the starch-grains are surrounded by a layer of cellulose or cellulose-like material that resists the action of ptyalin. When boiled, this layer breaks and the starch in the interior becomes exposed. In addition, the starch itself is changed during the boiling; it takes up water, and in this hydrated condition is acted upon more rapidly by the ptyalin. The practical value of cooking vegetable foods is evident from these statements without further comment.

**Physiological Value of Saliva.**—Although human saliva contains ptyalin, and this enzyme is known to possess very energetic amylolytic properties, yet it is probable that it has an insignificant action in normal digestion. The time that food remains in the mouth is altogether too short to suppose that the starch is profoundly affected by the ptyalin. Indeed, the saliva of dogs and cats is said to contain no ptyalin, while horse's saliva is free from ptyalin, although it contains a zymogen that may give rise to ptyalin. It would seem that what-

ever change takes place must be confined to the initial stages. After the mixed saliva and food are swallowed it is usually supposed that the acid reaction of the gastric juice soon stops completely all further amylolytic action, although this point is often disputed.<sup>1</sup> The complete digestion of the carbohydrates takes place after the food (chyme) has reached the small intestine, under the influence of the amylase of the pancreatic secretion. For these reasons it is usually believed that the main value of the saliva, to the human being and to the carnivora at least, is that it facilitates the swallowing of food. It is impossible to swallow perfectly dry food. The saliva, by moistening the food, not only enables the swallowing act to take place, but its viscous consistency must aid also in the easy passage of the food along the oesophagus. In addition the solution of parts of the food in the saliva gives occasion for the stimulation of the taste nerves, and, as we shall see in studying the mechanism of gastric secretion, the conscious sensations thus produced are very important for gastric digestion.

### C. GASTRIC DIGESTION.

After the food reaches the stomach it is exposed to the action of the secretion of the gastric mucous membrane, known usually as the *gastric juice*. The physiological mechanisms involved in the production and regulation of this secretion, and the important part played in gastric digestion by the movements of the stomach, will be found described in other sections (Secretion, Movements of Alimentary Canal). It is sufficient here to say that the secretion of gastric juice begins with the entrance of food into the stomach. By means of the muscles of the stomach the contained food is kept in motion for several hours and is thoroughly mixed with the gastric secretion, which during this time is exerting its digestive action upon certain of the food-stuffs. From time to time portions of the liquefied contents, known as *chyme*, are forced into the duodenum, and their digestion is completed in the small intestine. Gastric digestion and intestinal digestion go more or less hand in hand, and usually it is impossible to tell in any given case just how much of the food will undergo digestion in the stomach and how much will be left to the action of the intestinal secretions. It is possible, however, to collect the gastric secretion or to make an artificial juice and to test its action upon food-stuffs by digestions *in vitro*. Much of our fundamental knowledge of the digestive action of the gastric juice has been obtained in this way, although this has been supplemented, of course, by numerous experiments upon lower animals and human beings.

**Methods of Obtaining Normal Gastric Juice.**—The older methods used for obtaining normal gastric juice were very unsatisfactory. For instance, an animal was made to swallow a clean sponge to which a string was attached so that the sponge could afterward be removed and its contents be squeezed out; or there was given the animal to eat some indigestible material, to start the secretion of juice by mechanical stimulation, the animal being killed at the

<sup>1</sup> Austin: *Boston Medical and Surgical Journal*, 1899.



proper time and the contents of its stomach being collected. A better method of obtaining normal juice was suggested by the famous observations of Beaumont<sup>1</sup> upon Alexis St. Martin. St. Martin, by the premature discharge of his gun, was wounded in the abdomen and stomach. On healing, a fistulous opening remained in the abdominal wall, leading into the stomach, so that the contents of the latter could be inspected. Beaumont made numerous interesting and most valuable observations upon his patient. Since that time it has become customary to make fistulous openings into the stomachs of dogs whenever it is necessary to have the normal juice for examination. A silver canula is placed in the fistula, and at any time the plug closing the canula may be removed and gastric juice be obtained. In some cases the cesophagus has been occluded or excised so as to prevent the mixture of saliva with the gastric juice. Gastric juice may be obtained from human beings also in cases of vomiting or by means of the stomach-pump, but in such cases it is necessarily more or less diluted or mixed with food and cannot be used for exact analyses, although specimens of gastric juice obtained by these methods are valuable in the diagnosis and treatment of gastric troubles.

**Properties and Composition of Gastric Juice.**—The normal gastric secretion is a thin, colorless or nearly colorless liquid with a strong acid reaction and a characteristic odor. Its specific gravity varies, but it is never great, the average being about 1002 to 1003. Upon analysis the gastric juice is found to contain a trace of proteid, probably a peptone, some mucin, and inorganic salts, but the essential constituents are an acid (HCl) and two enzymes, pepsin and rennin. A satisfactory analysis of the human juice has not been reported, owing to the difficulty of getting proper specimens. According to Schmidt,<sup>2</sup> the gastric juice of dogs, free from saliva, has the following composition, given in 1000 parts:

Water . . . . .	973.0
Solids . . . . .	27.0
Organic substances . . . . .	17.1
Free HCl . . . . .	3.1
NaCl . . . . .	2.5
CaCl <sub>2</sub> . . . . .	0.6
KCl . . . . .	1.1
NH <sub>4</sub> Cl . . . . .	0.5
Ca <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub> . . . . .	1.7
Mg <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub> . . . . .	0.2
FePO <sub>4</sub> . . . . .	0.1

Gastric juice does not give a coagulum upon boiling, but the digestive enzymes are thereby destroyed. One of the interesting facts about this secretion is the way in which it withstands putrefaction. It may be kept for a long time, for months even, without becoming putrid and with very little change, if any, in its digestive action or in its total acidity. This fact shows that the juice possesses antiseptic properties, and it is usually supposed that the presence of the free acid accounts for this quality.

<sup>1</sup> *The Physiology of Digestion*, 1833.

<sup>2</sup> Hammarsten: *Text-book of Physiological Chemistry*, translated by Mandel, 1893, p. 177.

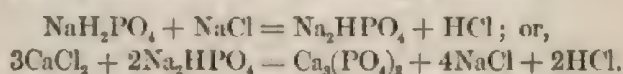
**The Acid of Gastric Juice.**—The nature of the free acid in gastric juice was formerly the subject of dispute, some claiming that the acidity is due to HCl, since this acid can be distilled off from the gastric juice, others contending that an organic acid, lactic acid, is present in the secretion. All recent experiments tend to prove that the acidity is due to HCl. This fact was first demonstrated satisfactorily by the analyses of Schmidt, who showed that if, in a given specimen of gastric juice, the chlorides were all precipitated by silver nitrate and the total amount of chlorine was determined, more was found than could be held in combination by the bases present in the secretion. Evidently, some of the chlorine must have been present in combination with hydrogen as hydrochloric acid. Confirmatory evidence of one kind or another has since been obtained. Thus it has been shown that a number of color tests for free mineral acids react with the gastric juice: methyl-violet solutions are turned blue, congo-red solutions and test-paper are changed from red to blue, OO tropaeolin from a yellowish to a pink-red, and so on. A number of additional tests of the same general character will be found described in the laboratory handbooks of physiology.<sup>1</sup> It must be added, however, that lactic acid undoubtedly occurs, or may occur, in the stomach during digestion. Its presence is usually explained as being due to the fermentation of the carbohydrates, and it is therefore more constantly present in the stomach of the herbivora. The amount of free acid varies according to the duration of digestion; that is, the secretion does not possess its full acidity in the beginning, owing probably to the fact (Heidenhain) that in the first periods of digestion, while the secretion is still scanty in amount, a portion of its acid is neutralized by the swallowed saliva and the alkaline secretion of the pyloric end of the stomach (see the section on Secretion). Estimates of the maximum acidity in the human stomach are usually given as between 0.2 and 0.3 per cent. The acidity of the dog's gastric juice is greater—0.46 to 0.56 per cent. (Pawlow).

**Origin of the HCl.**—The gastric juice is the only secretion of the body containing a free acid. The fact that the acid is a mineral acid makes this circumstance more remarkable, although other instances of a similar kind are known; for example, *Dolium galea*, a mollusc, secretes a salivary juice containing free  $H_2SO_4$  and free HCl. When and how the HCl is formed in the stomach is still a subject of investigation. Histologically, attempts have been made to show that it is produced in the border cells of the peptic glands in the fundic end of the stomach (see Secretion). It cannot be said, however, that the evidence for this theory is at all convincing; it can be accepted only provisionally. Ingenious efforts have been made to determine the place of production of the acid by micro-chemical methods. Substance that give color reactions with acids have been injected into the blood, and sections of the mucous membrane of the stomach have then been made to determine microscopically the part of the gastric glands in which the acid is produced; but beyond proving that the acid is formed in the mucous membrane these experiments have given negative results, the color reaction for acid occurring throughout the thickness of the

<sup>1</sup> Stirling: *Outlines of Practical Physiology*.



membrane.<sup>1</sup> The chemistry of the production of free HCl also remains undetermined. No free acid occurs in the blood or the lymph, and it follows, therefore, that it is manufactured in the secreting cells. It is quite evident, too, that the source of the acid is the neutral chlorides of the blood; these are in some way decomposed, the chlorine uniting with hydrogen to form HCl which is turned out upon the free surface of the stomach, while the base remains behind and probably passes back into the blood. The latter part of the process, the passage of the base into the blood-current, enables us to explain in part the facts, noticed by a number of observers, that the alkalinity of the blood is increased and the acidity of the urine is decreased after meals. Attempts to express the reaction that takes place in the decomposition of the chlorides are still too theoretical to merit more than a brief mention in a book of this character. According to Heidenhain, the cells secrete a free organic acid, which then acts upon and decomposes the chlorides. According to Maly, the HCl is the result of a reaction between the phosphates and the chlorides of the blood, as expressed in the two following equations:



A recent theory by Liebermann supposes that the mass action of the CO<sub>2</sub> formed in the tissues of the gastric mucous membrane upon the chlorides, with the aid of a nucleo-albumin of acid properties that can be isolated from the gastric glands, may account for the production of the HCl. Although it is customary to speak of the HCl as existing in a free state in the gastric juice, certain differences in reaction between this secretion and aqueous solutions of the same acidity have led to the suggestion that the HCl, or a part of it at least, is held in some sort of combination with the organic (proteid) constituents of the secretion, so that its properties are modified in some minor points just as the properties of haemoglobin are modified by the combination in which it is held in the corpuscles. The differences usually described are that in the gastric juice or in mixtures of HCl and proteid the acid does not dialyze nor distil off so readily as in simple aqueous solutions. The peptones and proteoses formed during digestion seem to combine with the acid very readily—so much so, in fact, that in certain cases specimens of gastric juice taken from the stomach, although they give an acid reaction with litmus-paper, may not give the special color reactions for free mineral acids. In such cases, however, the acid may still be able to fulfil its part in the digestion of proteids.

**Nature and Properties of Pepsin.**—Pepsin is a typical proteolytic enzyme that exhibits the striking peculiarity of acting only in acid media; hence peptic digestion in the stomach is the result of the combined action of pepsin and HCl. Pepsin is influenced in its action by temperature, as is the case with the other enzymes; low temperatures retard, and may even suspend, its activity, while high temperatures increase it. The optimum temperature is stated to be from 37° to 40° C., while exposure for some time to 80° C. results, when the

<sup>1</sup> Fränkel: *Pflüger's Archiv für die gesammte Physiologie*, 1891, Bd. 48, S. 63.

*M. Abrams*

pepsin is in a moist condition, in the total destruction of the enzyme. Pepsin has never been isolated in sufficient purity for satisfactory analysis. It may be extracted, however, from the gastric mucous membrane by a variety of methods and in different degrees of purity and strength. The commercial preparations of pepsin consist usually of some form of extract of the gastric mucous membrane to which starch or sugar of milk has been added. Laboratory preparations are usually made by mincing thoroughly the mucous membrane and then extracting for a long time with glycerin. Glycerin extracts, if not too much diluted with water or blood, keep for an indefinite time. Purer preparations of pepsin have been made by what is known as "Brücke's method," in which the mucous membrane is minced and is then self-digested with a 5 per cent. solution of phosphoric acid. The phosphoric acid is precipitated by the addition of lime-water, and the pepsin is carried down in the flocculent precipitate. This precipitate, after being washed, is carried into solution by dilute hydrochloric acid, and a solution of cholesterin in alcohol and ether is added. The cholesterin is precipitated, and, as before, carries down with it the pepsin. This precipitate is collected, carefully washed, and then treated repeatedly with ether, which dissolves and removes the cholesterin, leaving the pepsin in aqueous solution. This method is interesting not only because it gives the purest form of pepsin, but also in that it illustrates one of the properties of this enzyme—namely, the readiness with which it adheres to precipitates occurring in its solutions. Pepsin illustrates very well two of the general properties of enzymes that have been described (p. 281): first, its action is incomplete, the accumulation of the products of digestion inhibiting further activity at a certain stage; and, secondly, a small amount of the pepsin, if given sufficient time and the proper conditions, will digest a very large amount of proteid.

**Artificial Gastric Juice.**—In studying peptic digestion it is not necessary for all purposes to establish a gastric fistula to get the normal secretion. The active agents of the normal juice are pepsin and acid of a proper strength; and, as the pepsin can be extracted and preserved in various ways, and the HCl can easily be made of the proper strength, an artificial juice can be obtained at any time which may be used in place of the normal secretion for many purposes. In laboratory experiments it is customary to employ a glycerin extract of the gastric mucous membrane, and to add a small portion of this extract to a large bulk of 0.2 per cent. HCl. The artificial juice thus made, when kept at a temperature of from 37° to 40° C., will digest proteids rapidly if the preparation of pepsin is a good one. While the strength of the acid employed is generally from 0.2 to 0.3 per cent., digestion will take place in solutions of greater or less acidity. Too great or too small an acidity, however, will retard the process; that is, there is for the action of the pepsin an optimum acidity which lies somewhere between 0.2 and 0.5 per cent. Other acids may be used in place of the HCl—for example, nitric, phosphoric, or lactic—although they are not so effective, and the optimum acidity is different for each; for phosphoric acid it is given as 2 per cent.

**Action of Pepsin-Hydrochloric Acid on Proteids.**—It has been known for a long time that solid proteids, such as boiled eggs, when exposed to the



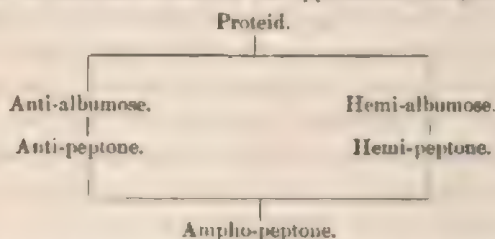
action of a normal or an artificial gastric juice, swell up and eventually pass into solution. The soluble proteid thus formed was known not to be coagulated by heat; it was remarkable also for being more diffusible than other forms of soluble proteids, and was further characterized by certain positive and negative reactions that will be described more explicitly farther on. This end-product of digestion was formerly described as a soluble proteid with properties fitting it for rapid absorption, and the name of *peptone* was given to it. It was quickly found, however, that the process was complicated—that in the conversion to so-called “peptone” the proteid under digestion passed through a number of intermediate stages. The intermediate products were partially isolated and were given specific names, such as *acid-albumin*, *parapeptone*, and *propeptone*. The two latter names, unfortunately, have not always been used with the same meaning by authors, and latterly they have fallen somewhat into disuse, although they are still frequently employed to indicate some one or other of the intermediate stages in the formation of peptones. The most complete investigation of the products of peptic digestion, and of proteolytic digestion in general, we owe to Kühne and to those who have followed along the lines he laid down, among whom may be mentioned Chittenden and Neumeister. Their work has thrown new light upon the whole subject and has developed a new nomenclature. In our account of the process we shall adhere to the views and terminology of this school, as they seem to be generally adopted in most of the recent literature. It is well, however, to add, by way of caution, that investigations of this character are still going on, and the views at present accepted are liable, therefore, to changes in detail as our experimental knowledge increases. Without giving the historical development of Kühne's theory, it may be said that at present the following steps in peptic digestion have been described: The proteid acted upon, whether soluble or insoluble, is converted first to an acid-albumin (see Chemical section) to which the name *syntonin* is usually given. In artificial digestions the solid proteid usually swells first from the action of the acid, and then slowly dissolves. Syntonin has the general properties of acid-albumins, of which properties the most characteristic is that the albumin is precipitated upon neutralizing the solution with dilute alkali. If, in the beginning of a peptic digestion, the liquid is neutralized, a more or less abundant precipitate of syntonin will form, the quantity depending upon the stage of digestion. Syntonin in turn, under the influence of the pepsin, takes up water and undergoes hydrolytic cleavage, with the formation of several soluble proteids known together as *primary albumoses* or *proteoses*.<sup>1</sup> Each of these proteids again takes up water and undergoes cleavage, with the formation of a second set of soluble proteids known as *secondary proteoses*, in contradistinction to the primary proteoses, but to which the specific name of *deutero-*

<sup>1</sup> The term *protease* is used by some authors in place of the older name *albumose*, as it has a more general significance. According to this usage the name *albumose* is given to the proteoses formed from albumin, *globulose* to those formed from globulin, etc., while *protease* is a general term applying to the intermediate products from any proteid.

*proteoses* is given. Finally, the deutero-proteose, or more properly the deutero-proteoses, again undergo hydrolytic cleavage, with the formation of what are known as *peptones*. Peptic digestion can go no farther than the formation of peptones, but we shall find later that other proteolytic enzymes (trypsin, for example) are capable of splitting up a part of the peptones still further. The fact that trypsin can act upon only a part of the peptone shows that this latter substance is either a mixture of at least two separate although closely-related peptones, to which the names of *anti-peptone* and *hemi-peptone*<sup>1</sup> have been given, or it is a compound containing such hemi- and anti- groups, and capable, under the action of trypsin, of splitting, with the formation of hemi-peptone and anti-peptone (Neumeister). If we consider peptic digestion alone, this distinction is unnecessary. The final products of peptic digestion are therefore spoken of usually simply as peptones, although the name *ampho-peptone* is also frequently used to emphasize the fact that two distinct varieties of peptone are possibly present. This description of the steps in peptic digestion may be made more intelligible by the following schema, which is modified somewhat from that given by Neumeister:<sup>2</sup>

This comparatively simple schema must not be regarded as final. It seems quite probable that further study will show that the process of splitting is more complicated than is here represented,<sup>3</sup> but provisionally, at least, it

<sup>1</sup> Kühne's full theory of proteolytic digestion assumes that the original proteid molecule contains two atomic groups, the hemi- and the anti-group. Proteolytic enzymes split the molecule so as to give a hemi- and an anti-compound, each of which passes through a proteose stage into its own peptone. A condensed schema of the hypothetical changes would be as follows:



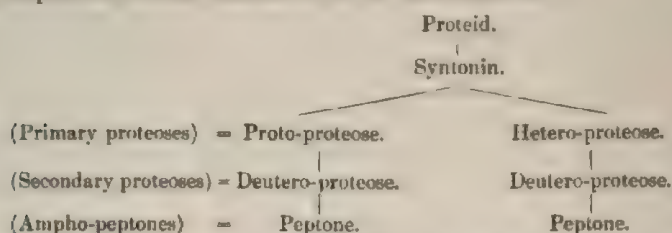
In the detailed description of proteolysis given above, primary and secondary proteoses are presumably, according to this schema, mixtures in varying proportions of hemi- and anti-compounds, or, in other words, they are *ampho-proteoses*. No good way of separating the anti- from the hemi-compounds has been discovered except to digest them with trypsin. By this means each compound is converted to its proper peptone, and by the continued action of the trypsin the hemi-peptone is split into much simpler bodies (p. 303), only anti-peptone being left in solution. The conception of a proteid molecule with hemi- and anti-groups and the splitting into hemi- and anti-albumose is mainly an inference backward from the fact that there are two distinct peptones, one of which, hemi-peptone, is acted upon by trypsin, while the other is not so acted upon. The details of the splitting of the proteid under the influence of pepsin are still further complicated by the fact that in some cases a part of the proteid remains undissolved, forming a highly resistant substance to which the name *antalbumid* has been given. It has been shown that if this substance is dissolved in sodium carbonate and then submitted to the action of trypsin, only anti-peptone is formed, indicating that it contains none of the hemi-group. In fact, the properties of antalbumid show that it is a peculiar modification of the anti-group which may arise during the cleavage of the proteid molecule, and may vary greatly in quantity in different digestions.

<sup>1</sup> *Lehrbuch der physiologischen Chemie*, 1893, p. 187.

<sup>2</sup> Consult Zünz: *Zeitschrift für physiologische Chemie*, Bd. 28, S. 132; and Pick, *Ibid.*, S. 219.



may be used to indicate the general nature of the process and to show some of the important details that seem to be determined.



According to this schema, peptic digestion, after the syntonin stage, consists in a succession of hydrolytic cleavages whereby soluble proteids (proteoses and peptones) are produced of smaller and smaller molecular weights. It is possible, of course, that the steps in this process may be more numerous than those represented in the schema, but the general nature of the changes seems to be established beyond question. Moreover, it is easy to understand that the products of digestion in any given case will vary with the stage at which the examination is made. Sufficiently early in the process one may find mainly syntonin, or syntonin and primary proteoses; later the secondary proteoses and peptones may occur alone or with traces of the first products. It is worth emphasizing also that in artificial digestions with pepsin, no matter how long the action is allowed to go on, the final product is always a mixture of peptones and proteoses (deutero-proteose). Even when provision is made to dialyze off the peptone as it forms, thus simulating natural digestion, the final result, according to Chittenden and Amerman,<sup>1</sup> is still a mixture of proteose and peptone. The extent of peptic digestion in the body will be spoken of presently in connection with a résumé of the physiology of gastric digestion. In general, it may be said that from a physiological standpoint the object of the whole process is to get the proteids into a form in which they can be absorbed more easily. The properties and reactions of peptones and proteoses will be found stated in the Chemical section. It may serve a useful end, however, to give here some of their properties, in order to emphasize the nature of the changes caused by the pepsin.

*Peptones.*—The name "peptones" was formerly given to all the products of peptic digestion after it had passed the syntonin stage—that is, to the proteoses as well as the true peptones. Commercially, the word is still used in this sense, the preparations sold as peptones being generally mixtures of proteoses and peptones. True peptones, in the sense used by Kühne, are distinguished chemically by certain reactions. Like the proteoses, they are very soluble, they are not precipitated by heating, and they give a red biuret reaction (see *Reactions of Proteids*, Chemical section). They are distinguished from the primary proteoses by not giving a precipitate with acetic acid and potassium ferrocyanide, and from the whole group of proteoses by the fact that they are not thrown down from their solutions by the most thorough saturation of the liquid with ammonium sulphate. This last reaction gives the only means for the complete

<sup>1</sup> *Journal of Physiology*, 1893, vol. xiv. p. 483.

separation of the peptones from the proteoses. The peptones, indeed, may be defined as being the products of proteolytic digestion which are not precipitated by saturation of the liquid with ammonium sulphate. The validity of this reaction has been called in question. It has been pointed out that, although the primary proteoses are readily precipitated by this salt, the deutero-proteoses, under certain circumstances at least, are not precipitated, and cannot therefore be distinguished or separated from the so-called "true peptones." We must await further investigations before attempting to come to any conclusion upon this point. It is well to bear in mind that the change from ordinary proteid to peptone evidently takes place through a number of intermediate steps, and the word *peptone* is meant to designate the final product. Whether this final product is a chemical individual with properties separating it from all the intermediate stages is perhaps not yet fully known, but, provisionally at least, we may adopt Kühne's definition, outlined above, of what constitutes peptone, as it seems to be generally accepted in current literature. Peptones are characterized by their diffusibility, and this property is also possessed, although to a less marked extent, by the proteoses. Recent work by Chittenden,<sup>1</sup> in which he corroborates results published simultaneously by Kühne, shows the following relative diffusibility of peptones and proteoses. The solutions used were approximately 1 per cent.; they were dialyzed in parchment tubes against running water for from six to eight hours, and the loss of substance was determined and expressed in percentages of the original amount. Proto-proteose gave a loss of 5.09 per cent.; deutero-proteose, 2.21 per cent.; peptone, 11 per cent.

*Rennin*.—In addition to pepsin the gastric secretion contains an enzyme that is characterized by its coagulating action upon milk. It has long been known that milk is curdled by coming into contact with the mucous membrane of the stomach. Dried mucous membrane of the calf's stomach, when stirred in with fresh milk, will curdle the latter with astonishing rapidity, and this property has been utilized in the manufacture of cheese. Hammarsten discovered that this action is due to the presence of a specific enzyme that exists ready formed in the membrane of the sucking-calf's stomach, and which is present in a preparatory form (rennin-zymogen) in stomachs of all mammals. This enzyme has been given several names; *rennin* seems preferable to any other, and is the term most commonly employed. Rennin may be obtained from the stomach by self-digestion of the mucous membrane or by extracting it with glycerin. Such extracts usually contain both pepsin and rennin, but the two have been separated successfully, most easily by the prolonged action of a temperature of 40° C. in acid solutions, which destroys the rennin, but not the pepsin. Good extracts of rennin cause clotting of milk with great rapidity at a temperature of 40° C., the milk (cow's milk), if undisturbed, setting first into a solid clot, which afterward shrinks and presses out a clear yellowish liquid, the whey; with human milk, however, the curd is much less firm, being deposited in the form of loose flocculi. The whole process resembles the clotting of blood not only in the superficial phenomena, but also in the character of the chemical changes. Briefly, what happens is that the rennin

<sup>1</sup> *Journal of Physiology*, 1893, vol. xiv. p. 502.



acts upon a soluble proteid in the milk known usually as *casein*, but by some called "caseinogen," and changes this proteid to an insoluble modification which is precipitated as the curd. The chemistry of the change is not completely understood, and there is an unfortunate want of agreement in the terminology used to designate the products of the action. It has been shown that, as in the case of blood, curdling cannot take place unless lime salts are present. What seems to occur is as follows: Casein is a complex substance belonging to the group of nucleo-proteids, and when acted upon by rennin it undergoes hydrolytic cleavage, with the formation of two proteid bodies, paracasein and whey proteid. The first of these bodies forms with calcium salts an insoluble compound which is precipitated as the curd; the second remains behind in solution in the whey. It should be added that casein is also precipitated from milk by the addition of an excess of acid. The curdling of sour milk in the formation of *bonnyclabber* is a well-known illustration of this fact. When milk stands for some time the action of bacteria upon the milk-sugar leads to the formation of lactic acid, and when this acid reaches a certain concentration it causes the precipitation of the casein. One might suppose that the curdling of milk in the stomach is caused by the acid present in the gastric secretion, but it has been shown that perfectly neutral extracts of the gastric mucous membrane will curdle milk quite readily.

So far as our positive knowledge goes, the action of rennin is confined to milk. Casein constitutes the chief proteid constituent of milk, and has therefore an important nutritive value. It is interesting to find that before its peptic digestion begins the casein is acted upon by an altogether different enzyme. The value of the curdling action is not at once apparent, but we may suppose that casein is more easily digested by the proteolytic enzymes after it has been brought into a solid form. The action of rennin goes no further than the curdling; the digestion of the curd is carried on by the pepsin, and later, in the intestines, by the trypsin, with the formation of proteoses and peptones as in the case of other proteids.

**Action of Gastric Juice on Carbohydrates and Fats.**—Human gastric juice itself has no direct action upon carbohydrates; that is, it does not contain an amylolytic enzyme. It is possible, nevertheless, that some digestion of carbohydrates goes on in the stomach, for, as has been seen, the masticated food is thoroughly mixed with saliva before it is swallowed. The portion that enters the stomach in the beginning of digestion, when the acidity of the total contents is small (see p. 289), may continue to be acted upon by the ptyalin. According to a recent author,<sup>1</sup> the gastric juice of the dog contains an amylolytic enzyme capable of acting on starch even in the presence of free HCl (0.5 per cent.). This statement needs confirmation, perhaps, and there is at present no evidence of the existence of a similar enzyme in the human gastric secretion. It should be added, however, that Lusk<sup>2</sup> has shown that cane-sugar can be inverted to dextrose and levulose in the stomach. The importance of this process of inversion, and the means by which it is accomplished, will be

<sup>1</sup> Friedenthal: *Archiv für Physiologie*, 1899; Suppl. Bd. 383.

<sup>2</sup> Voit: *Zeitschrift für Biologie*, 1891, Bd. xxviii. S. 269.

described more in detail when speaking of the digestion of sugars in the small intestine (p. 308). Upon the fats also gastric juice has no direct digestive action. According to the best evidence at hand, neutral fats are not split in the stomach, nor are they emulsified or absorbed. Without doubt, the heat of the stomach is sufficient to liquefy most of the fats eaten, and the movements of the stomach, together with the digestive action of its juice on the proteids and albuminoids with which the fats are often mixed, bring about such a mechanical mixture of the fats and oils with the other elements of the chyme as facilitates the more rapid digestion of these substances in the intestine.

**Action of Gastric Juice on the Albuminoids.**—Gelatin is, from a nutritive standpoint, the most important of the albuminoids. Its nutritive value is stated briefly on page 277. It has been shown that this substance is acted upon by pepsin in a way practically identical with that described for the proteids. Intermediate products are formed similar to the albumoses, which products have been named *gelatoses* or *glutoses*; these in turn may be converted to gelatin peptones. It is stated that the action of pepsin is confined almost, if not entirely, to changing gelatin to the gelatose stage. The proteolytic enzyme of the pancreatic secretion, however carries the change to the peptone stage much more readily.

**Why does the Stomach not Digest Itself?**—The gastric secretion will readily digest a stomach taken from some other animal, or under certain conditions it may digest the stomach in which it is secreted. If, for instance, an animal is killed while in full digestion, the stomach may undergo self-digestion, especially if the body is kept warm. This phenomenon has been observed in human cadavers. It has been shown also that if a portion of the stomach is deprived of its circulation by an embolism or a ligature, it may be attacked by the secretion and a perforation of the stomach-wall may result. How, then, under normal conditions, is the stomach protected from corrosion by its own secretion? The question has given rise to much discussion, and in reality it deals with one of the fundamental properties of living matter, for the same question must be extended to take in the non-digestion of the small intestine by the alkaline pancreatic secretion, the non-digestion of the digestive tracts of the invertebrates, and the case of the unicellular animals in which there is formed within the animal's protoplasm a digestive secretion that digests foreign material, but does not affect the living substance of the cell. In the particular case under consideration—namely, the protection of the mammalian stomach from its own secretion—explanations of the following character have been offered: It was suggested (Hunter) that the "principle of life" in living things protected them from digestion. This suggestion cannot be considered seriously at the present day, since it implies that living matter is the seat of a special force, the so-called "vital principle," different from the forms of energy acting upon matter in general. Appeals of this kind to an unknown force in explanation of the properties of living matter are not now permissible in the science of physiology. Moreover, it was shown by Bernard that the hind leg of a living frog introduced into a dog's stomach through a fistula undergoes digestion. The same thing will



happen, it may be added, if the leg is put into a vessel containing an artificial gastric juice at the proper temperature. Bernard's theory was that the epithelium of the stomach acts as a protection to the organ, preventing the absorption of the juice. Others believe that the mucus formed by the gastric membrane acts as a protective covering; while still another theory holds that the alkaline blood circulating through the organ saves it from digestion, since it neutralizes the acid of the secretion as fast as it is absorbed, and it is known that pepsin can digest only in an acid medium. None of these explanations is sufficient. The last explanation is unsatisfactory because it does not explain the immunity of the small intestine from digestion by the alkaline pancreatic juice, or the protection of the infusoria from their own digestive secretion. The mucous theory is inadequate, as we cannot believe that by this means the protection could be as complete as it is; and, moreover, this theory does not admit of a general application to other cases. The epithelium theory simply changes the problem a little, as it involves an explanation of the immunity of the living epithelial cells. It is well known that in the dead stomach the epithelial lining is no longer a protection against digestion, so that we are led to believe that there is nothing peculiar in the composition of epithelial cells, as compared with other tissues, to account for their exemption under normal conditions. When we come to consider all the evidence, nothing seems clearer than that the protection of the living tissue is in every case due to the properties of its living structure. So long as the tissue is alive, it is protected from the action of the digesting secretion, but the ultimate physical or chemical reason for this property is yet to be discovered. In the case of the mammalian stomach it is quite probable that the lining epithelial cells are especially modified to resist the action of the digestive secretion, but, as has just been said, they lose this property as soon as they undergo the change from living to dead structure. The digestion of the living frog's leg in gastric juice, and similar instances, do not affect this general idea, since, as Bernard himself pointed out, what happens in this case is that the tissue is first killed by the acid and then undergoes digestion. On the other hand, Neumeister has shown that a living frog's leg is not digested by strong pancreatic extracts of weak alkaline reaction, since under these conditions the tissues are not injured by the slightly alkaline liquid. When it is said that the exemption of living tissues from self-digestion is due to the peculiarities of their structure, it must not be supposed that this is equivalent to referring the whole matter to the action of a mysterious vital force. On the contrary, all that is meant is that the structure of living protoplasmic material is such that the action of the digestive secretion is prevented, possibly because it is not absorbed, this result being the outcome of the physical and chemical forces exhibited by matter with this peculiar structure. While a statement of this kind is not an explanation of the facts in question, and indeed amounts to a confession that an explanation is not at present possible, it at least refers the phenomenon to the action of known properties of matter.

**General Remarks upon Gastric Digestion.**—From the foregoing

account it will be seen that, speaking generally, the digestive functions of the stomach are in part to act chemically upon the proteids, and in part, by the combined action of its secretion and its muscular movements, to get the food into a physical condition suitable for subsequent digestion in the intestine. The material sent out from the stomach (chyme) must be quite variable in composition, but physically the action of the stomach has been such as to reduce it to a liquid or semi-liquid consistency. The extent of the true digestive action of gastric juice on proteids is not now believed to be so complete as it was formerly thought to be. Examination of the chyme shows that it may contain quantities of undigested or only partially digested proteid, complete digestion being effected in the intestines. Moreover, artificial peptic digestion of proteids under the most favorable conditions shows that only a portion is ever converted to peptone, most of it remaining in the proteose stage. It has been suggested, therefore, that gastric digestion of proteids is largely preparatory to the more complete action of the pancreatic juice, whose enzyme (trypsin) has more powerful proteolytic properties. In accordance with this idea, it has been shown that an animal can live and thrive without a stomach. Several cases<sup>1</sup> are on record in which the stomach was practically removed by surgical operations, the œsophagus being stitched to the duodenum. The animals did well and seemed perfectly normal. Experiments of this character do not, of course, show that the stomach is useless in digestion; they demonstrate only that in the animals used it is not absolutely essential. The reason for this will better be appreciated after the digestive properties of pancreatic secretion have been studied.

#### D. INTESTINAL DIGESTION.

After the food has passed through the pyloric orifice of the stomach and has entered the small intestine it undergoes its most profound digestive changes. Intestinal digestion is carried out mainly while the food is passing through the small intestine, although, as we shall see, the process is completed during the slower passage through the large intestine. Intestinal digestion is effected through the combined action of three secretions—namely, the pancreatic juice, the bile, and the intestinal juice. The three secretions act together upon the food, but for the sake of clearness it is advisable to consider each one separately as to its properties and its digestive action.

**Composition of Pancreatic Juice.**—Pancreatic juice is the secretion of the pancreatic gland. In man the main duct of the gland opens into the duodenum, in common with the bile-duct, about 8 to 10 cm. below the opening of the pylorus. In some of the other mammals the arrangement is different: in dogs, for example, there are two ducts, one opening into the duodenum, together with the bile-duct, about 3 to 5 cm. below the opening of the pylorus, and one some 3 to 5 cm. farther down. In rabbits the principal duct opens separately into the duodenum about 35 cm. below the opening of the bile-duct. For details as to the act of secretion, its time-relations to

<sup>1</sup> Ludwig and Ogata: *Archiv für Anatomie und Physiologie*, 1883, 8, 80; and Carvalho and Pachon: *Archives de Physiologie normale et pathologique*, 1894, p. 106.



the ingestion of food, its quantity, etc., the reader is referred to the section on Secretion. Most of our exact knowledge of the properties of the pancreatic secretion has been obtained either from experiments upon lower animals, especially the dog and the rabbit, in which it is possible to establish a pancreatic fistula and to collect the normal juice, or from experiments with artificial pancreatic juice prepared from extracts of the gland. Various methods have been used in making pancreatic fistulae: usually the main duct of the gland, which in the two animals named is separate from the bile-duct, is exposed and a canula is inserted. A better method, devised by Heidenhain, consists in cutting out the piece of duodenum into which the main duct opens and sewing this isolated piece to the abdominal wall so as to make a permanent fistula, the continuity of the intestinal tract in this case being re-established, of course, by sutures. A simple method of obtaining normal pancreatic juice from the rabbit is described by Ratchford.<sup>1</sup> In his method the portion of the duodenum into which the main duct opens is resected and cut open along the border opposite to the mesenteric attachment. The mouth of the duct is seen as a small papilla projecting from the surface of the mucous membrane. Through the papilla a small glass canula may be passed into the duct, and the secretion, which flows slowly, may be collected for several hours. The total quantity obtainable by this means from a rabbit is small, but it is sufficient for the demonstration of some of the important properties of pancreatic juice, especially its action upon fats. As obtained by these methods, the secretion is found to be a clear, colorless, alkaline liquid. The secretion obtained from dogs is thick and glairy, and forms a coagulum upon standing, while that from rabbits is a thin, perfectly colorless liquid which does not form a clot. In dogs the secretion from a permanent fistula soon becomes thinner than it was when the fistula was first established, and this change in its consistency is accompanied by a corresponding variation in specific gravity. The specific gravity (dog) of the juice from a temporary fistula is given at 1030; from a permanent fistula, at 1010 to 1011. The secretion coagulates upon being heated, owing to the proteids held in solution, and it undergoes putrefaction very quickly, so that it cannot be kept for any length of time. The analysis of the secretion most frequently quoted is that given by C. Schmidt, as follows:

*Pancreatic Juice (Dog).*

Constituents.	Immediately after establishing fistula.	From permanent fistula.
Water . . . . .	900.76	980.45
Solids . . . . .	99.24	19.55
Organic substances . . . . .	90.44	12.71
Ash . . . . .	8.80	6.84
Sodium carbonate . . . . .	0.58	3.31
Sodium chloride . . . . .	7.35	2.50
Calcium, magnesium, and sodium phosphates . . . . .	0.53	0.08

The composition of normal human pancreatic juice has not been determined completely, owing to the rarity of opportunities of obtaining the secretion.

<sup>1</sup> *American Journal of Physiology*, 1899, vol. ii. p. 483.

Several partial analyses have been reported. According to Zawadsky,<sup>1</sup> the composition of the secretion in a young woman was as follows:

	In 1000 parts.
Water . . . . .	864.05
Organic substances . . . . .	132.51
Proteids . . . . .	92.05
Salts . . . . .	3.44

The organic substances held in the secretion are in part of an albuminous nature, since they coagulate upon heating, but the exact nature of the proteid or proteids has not been determined satisfactorily. The most important of the organic substances—the essential constituents, indeed, of the whole secretion—are three enzymes acting respectively upon the proteids, the carbohydrates, and the fats. The proteolytic enzyme is called “trypsin;” the amylolytic enzyme is described under different names: “amylapsin” is perhaps the best, and will be adopted in this section; for the fat-splitting enzyme we shall use the term “steapsin.” Owing to the presence of these enzymes the pancreatic secretion is capable of exerting a digestive action upon each of the three important classes of food-stuffs. It is said that the pancreatic juice contains also a coagulating enzyme, similar to rennin, capable of curdling milk.

**Trypsin.**—Trypsin is a more powerful proteolytic enzyme than pepsin. Unlike the latter, trypsin acts best in alkaline media, but it is effective also in neutral liquids, or even in solutions not too strongly acid. Trypsin is affected by changes in temperature like the other enzymes, its action being retarded by cooling and hastened by warming. There is, however, a temperature, that may be called the optimum temperature, at which the trypsin acts most powerfully; if, however, the temperature is raised to as much as 70° to 80° C., the enzyme is destroyed entirely. Trypsin has never been isolated in a condition sufficiently pure for analysis, so that its chemical composition is unknown. Extracts containing trypsin can be made from the gland very easily and by a variety of methods. The usual laboratory method is to mince the gland and to cover it with glycerin for some time. In using this and other methods for preparing trypsin extracts it is best not to take the perfectly fresh gland, but to keep it for a number of hours before using. The reason for this is that the enzyme exists in the fresh gland in a preparatory stage, a zymogen (see section on Secretion), which in this case is called “trypsinogen.” Upon standing, the latter is slowly converted to trypsin—a process that may be hastened by the action of dilute acids and by other means. An artificial pancreatic juice is prepared usually by adding a small quantity of the pancreatic extract to an alkaline liquid; the liquid usually employed is a solution of sodium carbonate of from 0.2 to 0.5 per cent. To prevent putrefactive changes, which come on with such readiness in pancreatic digestions, a few drops of an alcoholic solution of thymol may be added. A mixture of this kind, if kept at the proper temperature, digests proteids very rapidly, and most of our knowledge of the action of trypsin has been obtained from a study of the products of such digestions.

<sup>1</sup> *Centralblatt für Physiologie*, 1891, Bd. v. S. 179.



**Products of Tryptic Digestion.**—Tryptic digestion resembles peptic digestion in that proteoses and peptones are the chief products formed, but the two processes differ in a number of details. The naked-eye appearances, in the first place, are different in cases in which the proteid acted upon is in a solid form; for while in the pepsin-hydrochloric digestion the proteid swells up and gradually dissolves, under the action of trypsin it does not swell, but suffers erosion, as it were, the solid mass of proteid being eaten out until finally only the indigestible part remains, retaining the shape of the original mass, but falling into fragments when shaken. In the second place, the hydrolytic cleavages seem to be of a more intense nature. In peptic digestion, after the syntonin stage is passed, there is a gradual change to peptone through the intermediate primary and secondary proteoses. Under the influence of trypsin, according to the most recent experiments, the solid proteid undergoes a transformation directly to secondary proteoses (deutero-proteoses), the intermediate stages being skipped. It was formerly thought that the solid proteid was converted first into a soluble proteid, and that if the solution was alkaline some alkali-albumin was formed, precipitable by neutralization, and comparable to the syntonin of pepsin-hydrochloric digestion. This soluble proteid was thought to be split into proteoses of the hemi- and anti- groups which were then converted to the corresponding peptones, according to Kühne's schema (p. 293). There seems to be no doubt that with the proteid most frequently used in artificial digestion—namely, fibrin from coagulated blood—the first effect is a conversion to a soluble globulin-like form of proteid; but Neumeister finds that this does not happen with other proteids, and he thinks that in the case of fibrin it is not due to a true digestive action of trypsin, but to a partial solution of the fibrin by the inorganic salts in the liquid. In general, however, the preliminary stage of a soluble proteid is missed, as also is that of the primary proteoses. The proteid falls at once by hydrolytic cleavage into deutero-proteoses, and these in turn are transformed to peptones. Just at this point comes in one of the most characteristic differences between the action of pepsin and that of trypsin. Pepsin cannot affect the peptones further, but trypsin may act upon the supposed hemi-constituent and split it up, with the formation of a number of much simpler nitrogenous bodies, most of which are amido-acids. The final products of prolonged tryptic digestion are, first, a peptone which cannot further be decomposed by the enzyme and which constitutes what is known as *anti-peptone*,<sup>1</sup> and, second, a number of simpler organic substances, amido-

<sup>1</sup> In the account of tryptic digestion as in the case of pepsin the nomenclature of Kühne is adhered to. It should be stated, however, that of late years some doubt has been thrown upon the existence of an anti-peptone. Siegfried (*Archiv für Physiologie*, 1894) identifies it with a body to which he gives the name carnic acid, while Kutscher (*Zeitschrift für physiologische Chemie*, Bd. 25) finds that anti-peptone prepared by Kühne's method is at least a mixture, since it contains the bases lysin, arginin, and histidin. If it should be shown that what has been called anti-peptone is not a peptone at all, but a mixture of simpler bodies, then it would seem that the original basis of Kühne's theory would be destroyed. There would be no occasion for supposing the existence of hemi- and anti-groupings. The general scheme of digestion that has been developed by this theory, with its stages of proteoses and peptones, would not, however, be interfered with.

acids and nitrogenous bases, that come from the splitting of that part of the peptone which can be acted upon by the trypsin, and which constitutes what is known as *hemi-peptone*. It may be remarked in passing that hemi-peptone has not been isolated. Ampho-peptones containing both anti- and hemi-peptones are formed in peptic digestion, and they may be obtained from tryptic digestion if it is not allowed to go too far; anti-peptone, on the other hand, may be obtained from tryptic digestion which has been permitted to go on until the hemi-peptone has been completely destroyed, but no good method is known by which hemi-peptone can be isolated from solutions containing both it and the anti- form. The principal products formed by the breaking up of the hemi-peptone molecule under the influence of the trypsin can be formed in the laboratory by processes that are known to cause hydrolytic decompositions. It is probable, therefore, that these substances may be looked upon as products of the hydrolytic cleavage of hemi-peptone. They are of smaller molecular weight and of simpler structure than the peptone molecule from which they are formed. A tabular list of these bodies, modified from Gamgee,<sup>1</sup> is given. The list includes only those substances that have actually been isolated; it is possible that others exist:

*Final Products (other than Peptones) of the Action of Trypsin on Albuminous and Albuminoid Bodies.*

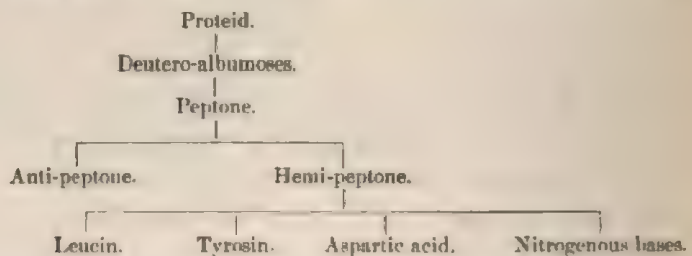
Bodies derived from the fatty acids.	Bases.	Organic body of unknown composition.	Aromatic bodies.
Iso-butyl amido-acetic acid (leucin).	Lysin.	Tryptophan (gives a red color on the addition of chlorine-water, and violet with bromine-water).	Paroxyphenylamidopropionic acid (tyrosin).
Amido-valerianic acid (chotalanin).	Histidin.		
Amido-succinic acid (aspartic acid).	Arginin.		
Amido-pyrotartaric acid (glutamic acid).	Lysatinin.		
(Diamido-acetic acid?)	NH <sub>3</sub> .		

Of these substances, the ones longest known and most easily isolated are leucin ( $C_6H_{13}NO_2$ ) and tyrosin ( $C_9H_{11}NO_3$ ). The chemical composition and properties of these and the other products are described in the Chemical section. Leucin and tyrosin have been found in the contents of the intestines, and it is probable, therefore, that the splitting of the peptone that takes place so readily in artificial tryptic digestions occurs also, to some extent at least, within the body, although we have no accurate estimates of the amount of peptone destroyed in this way under normal conditions. On the supposition that the production of leucin, tyrosin, and the other simple nitrogenous bodies is a normal result of tryptic digestion within the body, it is interesting to inquire what physiological value, if any, is to be attributed to these substances. At first sight, the formation of these simpler bodies from the valuable peptone would seem to be a waste. Peptone we know may be absorbed into the blood, and may then be used to form or repair proteid tissue, or to furnish energy to the

<sup>1</sup> *A Text-book of the Physiological Chemistry of the Animal Body*, 1893, vol. ii p. 230.



body upon oxidation, but leucin and tyrosin and the other products of the breaking up of peptone are far less valuable as sources of energy, and so far as we know they cannot be used to form or repair proteid tissue. But we must be careful not to jump too hastily to the conclusion that the splitting of the peptone is useless. It remains possible that a wider knowledge of the subject may show that the process is of distinct value to the body, although it must be confessed that no plausible suggestion as to its importance has yet been made. In addition to any possible functional value which these amidobodies and nitrogenous bases may possess, their occurrence in proteolysis is of immense interest to the physiologist. Some of them are of a constitution simple enough to be studied by exact chemical methods, and the hope is entertained that through them a clearer knowledge may be obtained of the structure of the proteid molecule. It should be added that not only are these bodies found in the alimentary canal as products of tryptic digestion, but that they, or some of them, occur also in other parts of the body, especially under pathological conditions, and that, furthermore, they occur among the products of the destruction of the proteid molecule by laboratory methods or by the action of bacterial organisms. The different stages in a complete tryptic digestion as outlined above are represented in brief in the following schema, modified from Neumeister :<sup>1</sup>



It may be said in conclusion that trypsin produces peptone from proteids more readily than does pepsin. Under normal conditions it is probable that most of the proteid of the food receives its final preparation for absorption in the small intestine, under the influence of this enzyme.

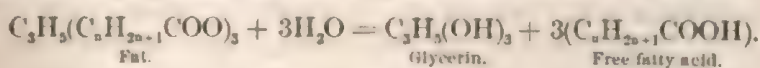
**Albuminoids.**—Gelatin and the other albuminoids are acted upon by trypsin, the products being similar in general to those formed from the proteids. As stated on page 297, pepsin carries the digestion of gelatin mainly to the gelatose stage; trypsin, however, produces gelatin peptones. It seems probable, therefore, that the final digestion of the albuminoids also is effected in the small intestine.

**Amylopsin.**—The enzyme of the pancreatic secretion that acts upon starches is found in extracts of the gland, made according to the general methods already given, and its presence may be demonstrated, of course, in the secretion obtained by establishing a pancreatic fistula. The proof of the existence of this enzyme is found in the fact that if some of the pancreatic secretion or some of the extract of the gland is mixed with starch paste, the

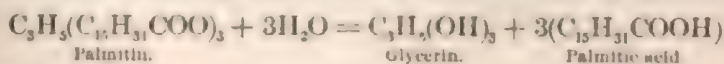
<sup>1</sup> *Lehrbuch der physiologischen Chemie*, 1893, S. 200.

starch quickly disappears and maltose or maltose and dextrin are found in its place. Amylopsin shows the general reactions of enzymes with relation to temperature, incompleteness of action, etc. Its specific reaction is its effect upon starches. Investigation has shown that the changes caused by it in the starches are apparently the same as those produced by ptyalin. In fact, the two enzymes ptyalin and amylopsin are identical in properties as far as our knowledge goes, so that it is not uncommon, in German literature especially, to have them both described under the name of *ptyalin*. The term *amylopsin* is convenient, however, in any case, to designate the special origin of the pancreatic enzyme. As to the details of its action, it is unnecessary to repeat what has been said on page 285. The end-products of its action, as far as can be determined from artificial digestions, are a sugar, maltose ( $C_{12}H_{22}O_{11}, H_2O$ ), and more or less of the intermediate achroödextrins, the relative amounts depending upon the completeness of digestion. As has previously been said, there are indications that under the favorable conditions of natural digestion all the starch may be changed to maltose, but possibly it is not necessary that the action should be so complete in order that the carbohydrate may be absorbed into the blood, as will be shown when we come to speak of the further action of the intestinal secretion upon maltose and the dextrins. The amylolytic action of the pancreatic juice is extremely important. The starches constitute a large part of our ordinary diet. The action of the saliva upon them is probably, for reasons already given, of subordinate importance. Their digestion takes place, therefore, entirely or almost entirely in the small intestine, and mainly by virtue of the action of the amylopsin contained in the pancreatic secretion. The action of the amylopsin is supplemented to some extent, apparently, by a similar enzyme formed in small quantities in the intestinal wall itself, the nature of which will be described presently in connection with intestinal secretion.

**Steapsin.**—Steapsin, or lipase, is the name given to a fat-splitting enzyme occurring in the pancreatic juice. It is of the greatest importance in the digestion and absorption of fats. The peculiar power of the pancreatic juice to split neutral fats with the liberation of free fatty acid was first described by Bernard. His discovery has since been corroborated for different animals, including man, by the use of normal pancreatic juice obtained from a fistula, or by the aid of the tissue of the fresh gland, or, finally, by means of extracts of the gland. When neutral fats (see Chemical section for the composition of fats) are treated with an extract containing steapsin, they take up water and then undergo cleavage (hydrolysis), with the production of glycerin and the free fatty acid found in the particular fat used. This reaction is explained by the following equation, in which a general formula for fats is used:



The reaction in the case of palmitin would be—





While this action is undoubtedly caused by an enzyme, it has not been possible to isolate the so-called "steapsin" in a condition of even approximate purity. As a matter of fact also, ordinary extracts of pancreas, such as the laboratory extracts in glycerin, do not usually show the presence of this enzyme unless special precautions are taken in their preparation. It would seem that steapsin is easily destroyed. With fresh normal juice or with pieces of fresh pancreas the fat-splitting effect can be demonstrated easily. One striking method of making the demonstration is to use butter as the fat to be decomposed. If butter is mixed with normal pancreatic juice or with pieces of fresh pancreas, and the mixture is kept at the body-temperature, the several fats contained in butter will be decomposed and the corresponding fatty acids will be liberated, among them butyric acid, which is readily recognized by its familiar odor, that of rancid butter. The action of steapsin, as in the case of the other enzymes, is very much influenced by the temperature. At the body-temperature the action is very rapid. The nature of the fat also influences the rapidity of the reaction; it may be said, in general, that fats with a high melting-point are less readily decomposed than those with a low melting-point. It has been shown, however, that even spermaceti, which is a body related to the fats and whose melting-point is  $53^{\circ}$  C., is decomposed, although slowly and imperfectly, by steapsin. The fat-splitting action of the steapsin undoubtedly takes place normally in the intestines, but it is questionable whether all the fat eaten undergoes this process. In fact, it may be said that two views are taught at present regarding the digestion and absorption of fats. According to the older view, only a certain small proportion of the fat undergoes splitting, or saponification, as it is sometimes called. The remainder of the fat becomes emulsified by the products (fatty acids) formed in the splitting, and are absorbed in an emulsified condition as neutral fats. According to the more recent view,<sup>1</sup> all the fat is supposed to be acted upon by the steapsin, with or without previous emulsification, with the formation of glycerin and fatty acids. These two products, the latter perhaps in part as a soap formed by reaction with the alkaline salts of the intestine, are absorbed in solution, and subsequently are recombined, probably in the substance of the epithelial cells, to form a neutral fat again. On both theories one of the first results of the action of the steapsin is the formation of an emulsion, the value of which on the first theory is that it brings the fat into a form in which it can be ingested by the epithelial cells of the villi, while on the second theory it consists in the fact that by subdividing the fat globules minutely the completion of the process of saponification is hastened. On either view, therefore, emulsification is an interesting preliminary to the absorption of fat, and some discussion of the nature of the process seems to be demanded.

**Emulsification of Fats.**—An oil is emulsified when it is broken up into minute globules that do not coalesce, but remain separated and more or less uniformly distributed throughout the medium in which they exist. Artificial emulsions can be made by shaking oil vigorously in viscous solutions

<sup>1</sup> Moore and Rockwood: *Journal of Physiology*, 1897, vol. 21 p. 58

of soap, mucilage, etc. Milk is a natural emulsion that separates partially on standing, some of the oil rising to the top to form cream. Bernard made the important discovery that when oil and pancreatic juice are shaken together an emulsion of the oil takes place very rapidly, especially if the temperature is about that of the body. The main cause of the emulsification has been shown to be the formation of free fatty acids due to the action of steapsin, and the union of these acids with the alkaline salts present to form soaps. This fact has been demonstrated by experiments of the following character: If a perfectly neutral oil is shaken with an alkaline solution ( $\frac{1}{4}$  per cent. sodium-carbonate solution), no emulsion occurs and the two liquids soon separate. If to the same neutral oil one adds a little free fatty acid, or if one uses rancid oil to begin with and shakes it with  $\frac{1}{4}$  per cent. sodium-carbonate solution, an emulsion forms rapidly and remains for a long time. Oil containing fatty acids when shaken with distilled water alone will not give an emulsion. It has been shown, moreover, by Gad and Ratchford that with a certain percentage of free fatty acids ( $5\frac{1}{2}$  per cent.) rancid oil and a sodium-carbonate solution will form a fine emulsion spontaneously—that is, without shaking. Shaking, however, facilitates the emulsification when the amount of free acid varies from this optimum percentage. In what way the formation of soaps in an oily liquid causes the oil to become emulsified is still a matter of speculation. The splitting of the oil into small drops seems to be caused, in cases of spontaneous emulsification, by the act of formation of the soap—that is, the union of the alkali with the fatty acid—in other cases by the mechanical shaking, or by these two causes combined. The application of these facts to the action of the pancreatic juice in the small intestine is easily made. When the chyme, containing more or less of liquid fat, comes into contact with the pancreatic juice, a part of the oil is quickly split by the steapsin, with the formation of free fatty acids. These acids unite with the alkalies and the alkaline salts present in the secretions of the small intestine (pancreatic juice, bile, intestinal juice) to form soaps. The formation of the soaps, aided, perhaps, by the peristaltic movements of the intestine, emulsifies the remainder of the fats and thus prepares them for absorption or further saponification. It has been suggested that the proteids in solution in the pancreatic juice aid in the emulsification, but there is no experimental evidence to show that this is the case. A factor of much more importance is the influence of the bile. In man the pancreatic juice and the bile are poured into the duodenum together, and in all mammals the two secretions are mixed with the food at some part of the duodenum. Now, it has been shown beyond question that a mixture of bile and pancreatic juice will cause a splitting of fats into fatty acids and glycerin much more rapidly than will the pancreatic juice alone.<sup>1</sup> This effect of the bile is not due to the presence in it of a fat-splitting enzyme of its own: the bile seems merely to favor in some way the action of the steapsin contained in the pancreatic secretion.

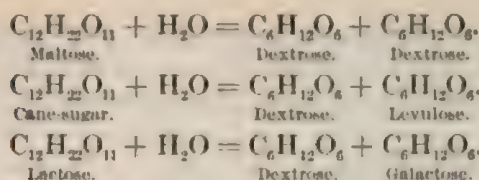
<sup>1</sup> Nencki: *Archiv für experimentelle Pathologie u. Pharmacologie*, 1886, Bd. 20, S. 367; Ratchford: *Journal of Physiology*, 1891, vol. 12, p. 27.



**Intestinal Secretion.**—The small intestine is lined with tubular glands, the crypts of Lieberkühn, that are supposed to form a secretion of considerable importance in digestion. To obtain the intestinal secretion, or *succus entericus*, as it is often called, recourse has been had to an ingenious operation for establishing a permanent intestinal fistula. This operation, which usually goes under the name of the "Thiry-Vella fistula," consists in cutting out a small portion of the intestine without injuring its supply of blood-vessels or nerves, and then sewing the two open ends of this piece into the abdominal wall so as to form a double fistula. The continuity of the intestines is established by suture, while the isolated loop with its two openings to the exterior can be used for collecting the intestinal secretion uncontaminated by partially-digested food. The secretion is always small in quantity, and it must be started by a stimulus of some kind. According to Röhmann,<sup>1</sup> it varies in quantity in different parts of the small intestine, being very scanty in the upper part and more abundant in the lower. The intestinal secretion is a yellowish liquid with a strong alkaline reaction. The reaction is due to the presence of sodium carbonate, the quantity of which is about 0.25 to 0.50 per cent. The chemical composition of the secretion has not been satisfactorily determined, but its digestive action has been investigated with success. Upon proteids and fats it is said to have no specific action—that is, it contains neither a proteolytic nor a fat-splitting enzyme. The possible value of its sodium carbonate in aiding the emulsification of fats has been referred to in the preceding paragraph. Upon carbohydrates the secretion has an important action. In the first place, it has been shown that it contains an amylolytic enzyme that is more abundant in the upper than in the lower part of the intestine. This enzyme doubtless aids the amylase of the pancreatic secretion in converting starches to sugar (maltose) or sugar and dextrin. What is still more important, however, is the presence of inverting enzymes (invertase) capable of converting cane-sugar (saccharose) into dextrose and levulose, and of a similar enzyme (maltase) capable of changing maltose to dextrose. Both of these effects are examples of the conversion of di-saccharides to mono-saccharides.

The di-saccharides of importance in digestion are cane-sugar, milk-sugar, and maltose. The first of these forms a common constituent of our daily diet; the second occurs always in milk; and the third, as we have seen, is the main end-product of the digestion of starches. These substances are all readily soluble, and we might expect that they would be absorbed directly into the blood without undergoing further change. As a matter of fact, however, it seems that they are first dissociated under the influence of the sugar-splitting enzymes into simpler mono-saccharide compounds, although in the case of lactose this statement is perhaps not entirely justified, our knowledge of the fate of this sugar during absorption being as yet incomplete. According to some authors, lactose is absorbed unchanged (see Chemical section). The general nature of this change is expressed in the three following reactions:

<sup>1</sup> *Pflüger's Archiv für die gesammte Physiologie*, 1887, Bd. 41, S. 411.



For the reactions by means of which these different isomeric forms of sugar are distinguished reference must be made to the Chemical section. The final stage in the artificial digestion of starches is the formation of maltose or of a mixture of maltose and dextrins. In the intestines, however, the process is carried a step farther by the aid of the sugar-splitting enzymes, and the maltose, and apparently the dextrins also, are converted into dextrose. According to this description, all of the starch is finally absorbed into the blood in the form of dextrose; and this conclusion falls in with the fact that the sugar found normally in the blood exists always in the form of dextrose. With reference to the sugar-splitting enzymes found in the small intestine, it should be added that they occur more abundantly in the mucous membrane than in the secretion itself. Indeed, the secretion is normally so scanty, especially in the upper part of the intestine, that it cannot be supposed to do more than moisten the free surface, and it is probable that the action of these enzymes takes place upon or in the mucous membrane, as the last step in the series of digestive changes of the carbohydrates immediately preceding their absorption.

**Digestion in the Large Intestine.**—Observations upon the secretions of the large intestine have been made upon human beings in cases of anus præternaturalis in which the lower portion of the intestine (rectum) was practically isolated. These observations, together with those made upon lower animals, unite in showing that the secretion of the large intestine is mainly composed of mucus, as the histology of the mucous membrane would indicate, and that it is very alkaline, and probably contains no digestive enzymes of its own. When the contents of the small intestine pass through the ileo-cæcal valve into the colon they still contain a quantity of incompletely digested material mixed with the enzymes of the small intestine. It is likely, therefore, that some at least of the digestive processes described above may keep on for a time in the large intestine; but the changes here of most interest are the absorption that takes place and the bacterial decompositions. The latter are described briefly below.

**Bacterial Decompositions in the Intestines.**—Bacteria of different kinds have been found throughout the alimentary canal from the mouth to the rectum. In the stomach, however, under normal conditions, the strong acid reaction prevents the action of those putrefactive bacteria that decompose proteids, and prevents or greatly retards the action of those that set up fermentation in the carbohydrates. Under certain abnormal conditions known to us under the general term of *dyspepsia*, bacterial fermentation of the carbohydrates may be pronounced, but this must be considered as pathological.



In the small intestine the secretions are all alkaline, and it was formerly taken for granted that the intestinal contents are normally alkaline. If this were so, the bacteria would find a favorable environment. It was supposed that putrefaction of the proteids might occur, especially during the act of tryptic digestion, and this supposition was borne out by the extraordinary readiness of artificial pancreatic digestions to undergo putrefaction when not protected in some way. Two recent cases<sup>1</sup> of fistula of the ileum at its junction with the colon in human beings have given opportunity for exact study of the contents of the small intestine. The results are interesting, and to a certain extent are opposed to the preconceived notions as to reaction and proteid putrefaction which have just been stated. They show that the contents of the intestine at the point where they are about to pass into the large intestine are acid, provided a mixed diet is used, the acidity being due to organic acids (acetic) and being equal to 0.1 per cent. acetic acid. These acids must have come from the bacterial fermentation of the carbohydrates, and a number of bacteria capable of producing such fermentation were isolated. The products of bacterial putrefaction of the proteids, on the contrary, were absent, and it has been suggested that the acid reaction produced by the fermentation of the carbohydrates serves the useful purpose, under normal conditions, of preventing the putrefaction of the proteids. With reference, therefore, to the point we are discussing—namely, the bacterial decomposition of the contents of the intestines—we may conclude, upon the evidence furnished by these two cases, that in the human being, when living on a mixed diet, some of the carbohydrates undergo bacterial decomposition in the small intestine, but that the proteids are protected. We may further suppose that in the case of the proteids the limits of protection are easily overstepped, and that such a condition as a large excess of proteid in the diet or a deficient absorption from the small intestine may easily lead to extensive intestinal putrefaction involving the proteids as well as the carbohydrates.

In the large intestine, on the contrary, the alkaline reaction of the secretion is more than sufficient to neutralize the organic acids arising from fermentation of the carbohydrates, and the reaction of the contents is therefore alkaline. Here, then, what remains of the proteids undergoes, or may undergo, putrefaction, and this process must be looked upon as a normal occurrence in the large intestine. The extent of the bacterial action upon the proteids as well as the carbohydrates may vary widely even within the limits of health, and if excessive may lead to intestinal troubles. Among the products formed in this way, the following are known to occur: Leucin, tyrosin, and other amido-acids; indol; skatol; phenols; various members of the fatty-acid series, such as lactic, butyric, and caproic acids; sulphuretted hydrogen; methane; hydrogen; methyl mercaptan, etc. Some of these products will be described more fully in treating of the composition of the feces. To what extent these products are of value to the body it is difficult, with our imperfect knowledge, to say. It has been pointed out, on the one hand, that some of them (skatol, fatty

<sup>1</sup> Macfayden, Nencki, and Sieber: *Archiv für experimentelle Pathologie u. Pharmacologie*, 1891, Bd. 23, S. 311; Jakowski: *Archives des Sciences biologiques*, St. Petersburg 1892, t. 1.

acids,  $\text{CO}_2$ ,  $\text{CH}_4$ , and  $\text{H}_2\text{S}$ ) promote the movements of the intestine, and may be of value from this standpoint; on the other hand, some of them are absorbed into the blood, to be eliminated again in different form in the urine (indol and phenols), and it may be that they are of importance in the metabolism of the body; but concerning this our knowledge is deficient. On the whole, we must believe that the food in its passage through the alimentary canal is acted upon mainly by the digestive enzymes, the so-called "unorganized" ferments, but that the action of the bacteria, or organized ferments, is responsible for a part of the changes that the food undergoes before its final elimination in the form of feces. These two kinds of action vary greatly within normal limits, and to a certain extent they seem to be in inverse relationship to each other. When the digestive enzymes and secretions are deficient or ineffective the field of action for the bacteria is increased, and this seems to be the case in some pathological conditions, the result being intestinal troubles of various kinds. The limits of normal bacterial action have not been worked out satisfactorily, but it is evident that our knowledge of digestion will not be complete until this is accomplished.

It should be stated in conclusion that, however constant and important the occurrence of bacterial fermentation may be in the alimentary canal, it cannot be regarded as essential to the life of the animal, since Nuttall and Theirfelder,<sup>1</sup> in a series of ingenious experiments made upon newly-born guinea-pigs, have shown that these animals may thrive, for a time at least, when the entire alimentary canal is free from bacteria.

#### E. ABSORPTION; SUMMARY OF DIGESTION AND ABSORPTION OF THE FOOD-STUFFS; FECES.

In the preceding sections we have followed the action of the various digestive secretions upon the food-stuffs as far as the formation of the supposed end-products. In order that these products may be of actual nutritive value to the body, it is necessary, of course, that they shall be absorbed into the circulation and thus be distributed to the tissues. There are two possible routes for the absorbed products to take: they may pass immediately into the blood, or they may enter the lymphatic system, the so-called "lacteals" of the alimentary canal. In the latter case they reach the blood finally before being distributed to the tissues, since the thoracic duct, into which the lymphatics of the alimentary canal all empty, opens into the blood-vascular system at the junction of the left internal jugular and subclavian veins. The substances that take this route are distributed to the tissues by the blood, but it is to be noticed that, owing to the sluggish flow of the lymph-circulation (see section on Circulation), a relatively long time elapses after digestion before they enter the blood-current. The products that enter the blood directly from the alimentary canal are distributed rapidly; but in this case we must remember that they first pass through the liver, owing to the existence of

<sup>1</sup> *Zeitschrift für physiologische Chemie*, 1895, Bd. 21; 1896, Bd. 22, and 1897, Bd. 23.



the portal circulation, before they reach the general circulation. During this passage through the liver, as we shall find, changes of the greatest importance take place. The physiology of absorption is concerned with the physical and chemical means by which the end-products of digestion are taken up by the blood or the lymph, and the relative importance of the stomach, the small intestine, and the large intestine in this process. Leaving aside the fats, whose absorption is a special case, the absorption of the other products of digestion was formerly thought to be a simple physical process. The processes of diffusion and osmosis, as they are known to occur outside the body, were supposed to account for the absorption of all the soluble products. This belief is still held by many, but the facts known with regard to the absorption of the carbohydrates, proteids, and fats after the changes undergone during digestion are not wholly accounted for by the laws of diffusion and osmosis as they are known to us (see p. 65 for a discussion of the nature of these processes). For the present at least it seems to be necessary to refer many of the phenomena of physiological absorption to the peculiar properties of the living epithelial cells lining the alimentary canal. Some of the important facts regarding absorption are as follows:

**Absorption in the Stomach.**—In the stomach it is possible that there might be absorption of the following substances: water; salts; sugars and dextrans that may have been formed in salivary digestion from starch, or that may have been eaten as such; the proteoses and peptones formed in the peptic digestion of proteids or albuminoids. In addition, absorption of soluble or liquid substances—drugs, alcohol, etc.—that have been swallowed may occur. It was formerly assumed without definite proof that the absorption in the stomach of such things as water, salts, sugars, and peptones was very important. Of late years a number of actual experiments have been made, under conditions as nearly normal as possible, to determine the extent of absorption in this organ. These experiments have given unexpected results, showing, upon the whole, that absorption does not take place readily in the stomach—certainly nothing like so easily as in the intestine. The methods made use of in these experiments have varied, but the most interesting results have been obtained by establishing a fistula of the duodenum just beyond the pylorus.<sup>1</sup> Through a fistula in this position substances can be introduced into the stomach, and if the cardiac orifice is at the same time shut off by a ligature or a small balloon, they can be kept in the stomach a given time, then be removed, and the changes, if any, be noted. After establishing the fistula in the duodenum food may be given to the animal, and the contents of the stomach as they pass out through the fistula may be caught and examined. The older methods of introducing the substance to be observed into the stomach through the œsophagus or through a gastric fistula were of little use, since, if the substance disappeared, there was no way of deciding whether it was absorbed or was simply passed on into the intestine.

<sup>1</sup> Compare von Mering: *Verhandl. des Congresses f. innere Med.*, 12, 471, 1893; Edkins: *Journal of Physiology*, 1892, vol. 13, p. 445; Brandl: *Zeitschrift für Biologie*, 1892, Bd. 29, S. 277.

**Water.**—Experiments of the character just described show that water when taken alone is practically not absorbed at all in the stomach. Von Mering's experiments especially show that as soon as water is introduced into the stomach it begins to pass out into the intestine, being forced out in a series of spurts by the contractions of the stomach. Within a comparatively short time practically all the water can be recovered in this way, none or very little having been absorbed in the stomach. For example, in a large dog with a fistula in the duodenum, 500 cubic centimeters of water were given through the mouth. Within twenty-five minutes 495 cubic centimeters had been forced out of the stomach through the duodenal fistula. The result was not true for all liquids; alcohol, for example, was absorbed readily.

**Salts.**—The absorption of salts from the stomach has not been investigated thoroughly. According to Brandl, sodium iodide is absorbed very slowly or not at all in dilute solutions. Not until its solutions reach a concentration of 3 per cent. or more does its absorption become important. This result, if applicable to all the soluble inorganic salts, would indicate that under ordinary conditions they are practically not absorbed in the stomach, since it cannot be supposed that they are normally swallowed in solutions so concentrated as 3 per cent. It was found that the absorption of sodium iodide was very much facilitated by the use of condiments, such as mustard and pepper, or alcohol, which act either by causing a greater congestion of the mucous membrane or perhaps by directly stimulating the epithelial cells.

**Sugars and Peptones.**—Experiments by the newer methods leave no doubt that sugars and peptones can be absorbed from the stomach. In Von Mering's work different forms of sugar—dextrose, lactose, saccharose (cane-sugar), maltose, and also dextrin—were tested. They were all absorbed, but it was found that absorption was more marked the more concentrated were the solutions. Brandl, however, reports that sugar (dextrose) and peptone were not sensibly absorbed until the concentration had reached 5 per cent. With these substances also the ingestion of condiments or of alcohol increased distinctly the absorptive processes in the stomach. On the whole it would seem that sugars and peptones are absorbed with some difficulty from the stomach.

**Fats.**—As we have seen, fats undergo no digestive changes in the stomach. The processes of saponification and emulsification are supposed to be preliminary steps to absorption, and, as these processes take place only after the fats have reached the small intestine, there seems to be no doubt that in the stomach fats escape absorption entirely.

**Absorption in the Small Intestine.**—The soluble products of digestion—sugars and peptones or proteoses, as well as the saponified and emulsified fats—are mainly absorbed in the small intestine. This we should expect from a mere *a priori* consideration of the conditions prevailing in this part of the alimentary canal. The partially-digested food sent out from the stomach meets the digestive secretions in the beginning of the small intestine. As we have seen, the different enzymes of the pancreatic secretion act powerfully upon the three important classes of food-stuffs, and we have every reason to believe that their digestion makes



rapid progress. The passage of the food along the small intestine, although rapid compared with its passage through the large intestine, requires a number of hours for its completion. According to the observations made upon a patient with a fistula at the end of the small intestine,<sup>1</sup> food begins to pass into the large intestine in from two to five and a quarter hours after it has been eaten, and it requires from nine to twenty-three hours before the last portions reach the end of the small intestine; this estimate includes, of course, the time in the stomach. During this progress it has been converted for the most part into a condition suitable for absorption, and the mucous membrane with which it is in contact is one peculiarly adapted for absorption, since its epithelial surface is greatly increased in extent by the vast number of villi as well as by the numerous large folds known as the "valvæ conniventes." In addition to these considerations, however, we have abundant experimental proof that absorption takes place actively in the small intestine. The absorption of fats can be demonstrated microscopically, as will be described presently. Experiments made by Röhmman<sup>2</sup> and others with isolated loops of intestine have shown that sugars and peptones are absorbed readily and in much more dilute solutions than in the stomach. Moreover, in the case just referred to, of an intestinal fistula at the end of the small intestine, a determination of the proteid present in the discharge from the fistula, after a test-meal containing a known amount of proteid, showed that about 85 per cent. had disappeared—that is, had been absorbed before reaching the large intestine. With reference to water and salts, it has been shown that they also are readily absorbed; some very interesting experiments demonstrating this fact have been reported by Heidenhain.<sup>3</sup> It must be remembered, however, that under normal conditions the absorption of water and salts is more or less compensated by the secretion formed along the length of the intestine, so that when the contents reach the ileo-cæcal valve they are still of a fluid consistency similar to that of the chyme when it left the stomach to enter the intestine. A consideration of the mechanism of the absorption of fats, sugars, peptones, and water will be taken up presently, after a few words have been said of absorption in the large intestine.

**Absorption in the Large Intestine.**—There can be no doubt that absorption forms an important part of the function of the large intestine. The contents pass through it with great slowness, the average duration being given usually as twelve hours, and while they enter through the ileo-cæcal valve in a thin fluid condition, they leave the rectum in the form of nearly solid feces. This fact alone demonstrates the extent of the absorption of water. As for the sugar and peptones, examination of the intestinal contents as they entered the large intestine in the case of fistula cited in the preceding paragraph showed that there may still be present an important percentage of proteid (14 per cent.) and a variable amount of sugars and fats—more than is

<sup>1</sup> Macfadyen, Nencki, and Sieber: *Archiv für experimentelle Pathologie u. Pharmacologie*, 1891, Bd. 28, S. 311.

<sup>2</sup> *Plüger's Archiv für die gesammte Physiologie*, 1887, Bd. 41, S. 411.

<sup>3</sup> *Ibid.*, 1894, Bd. 56, S. 637.

found normally in the feces. Some of this carbohydrate and proteid undergoes destruction by bacterial action, as has already been explained (p. 310), but some of it is absorbed, or may be absorbed, before decomposition occurs. The power of absorption in the large intestine has been strikingly demonstrated by the fact that various substances injected into the rectum are absorbed and suffice to nourish the animal. Enemata of this character are frequently used in medical practice with satisfactory results, and careful experimental work on lower animals and on men under conditions capable of being properly controlled has corroborated the results of medical experience and shown that even in the rectum absorption takes place. Without giving the details of this work, it may be said that it is now known that proteids in solution, or even such things as eggs beaten to a fluid mass with a little salt, are absorbed from the rectum, and this notwithstanding the fact that no proteolytic enzyme is found in this part of the alimentary canal. Fats also (such as milk-fat) and sugars can be absorbed in the same way. Some of these facts have been corroborated in a striking way by Harley<sup>1</sup> in experiments upon dogs from which he had removed the whole of the large intestine. It was found that in these animals there was an increase in the quantity of water in the feces, the total quantity being nearly five times as much as in the normal dog.

**Absorption of Proteids.**—As we have seen in the preceding paragraphs, absorption of proteids takes place in the stomach and the small and large intestines, but in all probability mainly in the small intestine. The end-products of the digestion of proteids by the proteolytic enzymes are proteoses and peptones. Tryptic digestion produces also leucin, tyrosin, and the related amido-bodies, but so far as proteid has undergone decomposition to this stage it is no longer proteid, and does not have the nutritive value of proteid. The logical conclusion from our knowledge of proteid digestion should be that all proteid is reduced to the form of proteoses or peptones before absorption, and that the great advantage of proteolysis is that proteids are more readily absorbed in this form than in any other. In the main we must accept this conclusion. The process of proteid digestion would seem to be without meaning otherwise. But we must not shut our eyes to the fact that proteid may be absorbed in other forms than peptones or proteoses. This has been demonstrated most clearly for the rectum and the lower part of the colon, as was stated in the preceding paragraph. Enemata of dissolved muscle-proteid (myosin), egg-albumin, etc. are absorbed from this part of the alimentary canal without, so far as can be determined, previous conversion to peptones and proteoses, and we must admit that the same power is possessed by other parts of the intestinal tract. It is probable, for instance, that the very first product of pepsin-hydrochloric digestion, syntonin, is capable of absorption directly. This fact, however, does not weaken the conclusion that peptones and proteoses are absorbed more easily than other forms of proteids, and that they constitute the form in which the bulk of our proteid is absorbed.

<sup>1</sup> *Proceedings of the Royal Society, London, 1899, vol. lxiv, No. 408.*



Opinions as to why these forms of proteids are more easily absorbed than any other must vary with the theory held as to the nature of absorption. Experiments have shown that proteoses and peptones are more easily diffusible than other forms of proteids, and this fact tends to support the view that their absorption is due to physical diffusion. The object of digestion, on this view, is to convert the insoluble and non-dialyzable proteids into soluble, diffusible peptones. But a study of the details of proteid absorption has shown that the process cannot be explained entirely by the laws of simple dialysis that govern the process of diffusion through dead membranes. Proteids, like egg-albumin, which are practically non-dialyzable are absorbed readily from the intestine. Moreover, when one considers the rate of absorption of peptone from the alimentary tract, it seems to be much too rapid and complete to be accounted for entirely by the diffusibility of this substance as determined by experiments with parchment dialyzers. It is believed, therefore, that the initial act in the absorption of proteids is dependent in some way upon the peculiar properties of the layer of living epithelial cells lining the mucous membrane. Whether the peculiarity is a physical one depending on some special structure of the cells that makes them permeable to the proteid molecules, or whether it is a more obscure and complicated process connected with the living activity of the cells, remains undetermined for the present. After the proteids have passed through the epithelium it is a matter of importance to determine whether they enter the blood or the lymph circulation. Experiments have shown conclusively that they are transmitted directly to the blood-capillaries: ligature of the thoracic duct, for example, which shuts off the entire lymph-flow coming from the intestine, does not interfere with the absorption of proteids. There is one other fact of great significance in connection with this subject: the proteids are absorbed mainly, if not entirely, as proteoses and peptones, and they pass immediately into the blood; nevertheless, examination of the blood directly after eating, while the process of absorption is in full activity, fails to show any peptones or proteoses in the blood. In fact, if these substances are injected directly into the blood, they behave as foreign, and even as toxic, bodies. In certain doses they produce insensibility with lowered blood-pressure, and they may bring on a condition of coma ending in death. Moreover, when present in the blood, even in small quantities, they are eliminated by the kidneys and are evidently unfit for the use of the tissues. It follows from these facts that while the peptones and proteoses are being absorbed by the epithelial cells they are at the same time changed into some other form of proteid. What this change is has not been determined. Experiments have shown that peptones disappear when brought into contact with fresh pieces of the lining mucous membrane of the intestine which are still in a living condition. The statement has been made that the peptones and proteoses are converted to serum-albumin, or at least to a native albumin of some kind, but we have no definite knowledge beyond the fact that the peptones and proteoses, as such, disappear. It is well to call attention to the

fact that the digestion of proteids is supposed, according to the schema already described, to consist in a process of hydration and splitting, with the formation, probably, of smaller molecules. The reverse act of conversion of peptones back to albumin implies, therefore, a process of dehydration and polymerization that presumably takes place in the epithelial cells. It is at this point in the act of absorption of proteids that our knowledge is most deficient.

**Absorption of Sugars.**—The carbohydrates are absorbed mainly in the form of sugar or of sugar and dextrin. Starches are converted in the intestine into maltose or maltose and dextrin, and then by the sugar-splitting enzymes of the mucous membrane are changed to dextrose. Ordinary cane-sugar is hydrolyzed into dextrose and levulose before absorption, and milk-sugar possibly undergoes a similar change to dextrose and galactose, though less is known of this. So far as our knowledge goes, then, we may say that the carbohydrates of our food are eventually absorbed in the form mainly of dextrose or of dextrose and levulose, leaving out of consideration, of course, the small part that normally undergoes bacterial fermentation. In accordance with this statement, we find that the sugar of the blood exists in the form of dextrose. It is apparently a form of sugar that can be oxidized very readily by the tissues. In fact, it has been shown that if cane-sugar is injected directly into the blood, it cannot be utilized, at least not readily, by the tissues, since it is eliminated in the urine; whereas if dextrose is introduced directly into the circulation, it is all consumed, provided it is not injected too rapidly. The sugars are soluble and dialyzable, but, as in the case of peptones, exact study of their absorption shows that it does not follow in detail the known laws of osmosis through dead membranes. Experiments indicate, however, that in a general way the behavior of solutions of sugar placed in isolated loops of the intestine may be understood by assuming that a diffusion takes place, and it may be therefore that the peculiarities observed are connected with the structure of the living epithelium. We have to deal here, in fact, with the same difficulty as was encountered in the case of the proteids. A special vital activity of the epithelial cells cannot be excluded, and we must be content to await a fuller development of experimental investigation before attempting to come to a final conclusion. As in the case of the proteids, the absorbed sugars—dextrose or dextrose and levulose—pass directly into the blood, and do not under normal conditions enter the lymph-vessels. This has been demonstrated by direct examination of the blood of the portal vein during digestion (von Mering<sup>1</sup>), a distinct increase in its sugar-contents being found. Examination of the lymph shows no increase in sugar unless excessive amounts of carbohydrates have been eaten (Heidenhain).

**Absorption of Fats.**—As has been stated, fats are absorbed either in solid form, as emulsified droplets, or as fatty acids or soaps. In the latter case the fatty acids are again recombined to particles of neutral fat, presumably within the substance of the epithelial cells. So far as the emulsified fat

<sup>1</sup> Du Bois-Reymond's *Archiv für Anatomie und Physiologie*, 1877, S. 413.



is concerned, the process of absorption must be of a mechanical nature. The details of the process have been worked out microscopically and have given rise to numerous researches. It is unnecessary to speak of the various theories that have been held, as it has been shown by nearly all the recent work that the immediate agent in the absorption of fats is again the epithelial cells of the villi of the small intestine. The fat-droplets may be seen within these cells, and can be studied microscopically after digestion in the act of passing, or rather of being passed, through the cell-substance. Reference to the histology of the villi will show that each villus possesses a comparatively large lymphatic capillary lying in its middle and ending blindly, apparently, near the apex of the villus. Between this central lymphatic—or lacteal, as it is called here—and the epithelium lies the stroma, or main substance of the villus, which, in addition to its blood-capillaries and plain muscle-fibres, consists mainly of lymphoid or adenoid tissue containing numerous leucocytes. The fat-droplets have to pass from the epithelium to the central lymphatic, for it is one of the most certain facts in absorption, and one which has been long known, that the fat absorbed gets eventually into the lacteals in an emulsified condition and thence is conveyed through the system of lymphatic vessels to the thoracic duct and finally to the blood. The name "lacteal," in fact, is given to the lymphatic capillaries of the villus on account of the milky appearance of their contents, after meals, caused by the emulsified fat. It should be added, however, that it has not been possible to demonstrate experimentally that all the absorbed fat passes into the thoracic duct. Attempts have been made to collect all the fat passing through the thoracic duct after a meal containing a known quantity of fat, but even after making allowance for the unabsorbed fat in the feces there is a considerable percentage of the fat absorbed that cannot be recovered from the lymph of the thoracic duct. While this result does not invalidate the conclusion stated above that the fat passes chiefly, perhaps entirely, into the lacteals, it does indicate that there are some factors concerned in the process of fat-absorption that are at present unknown to us. The passage of the fat-droplets to the central lacteal is not difficult to understand. The adenoid tissue of the stroma is penetrated by minute unformed lymph-channels that are doubtless connected with the central lacteal. In each villus lymph is continually formed from the circulating blood, so that there must be a slow stream of lymph through the stroma to the lacteal. When the fat-droplets have passed through the epithelial cells (and basement membrane) they drop into the interstices of the adenoid tissue and are carried in this stream into the lacteal. The lacteals were formerly designated as the "absorbents," under the false impression that they attended to all the absorption going on in the intestines, including that of peptones, sugars, and fats. It is now known that their action under ordinary conditions is limited to the absorption of fats.

**Absorption of Water and Salts.**—From what has been said (p. 312) it is evident that absorption of water takes place very slightly, if at all, in the stomach. Whenever soluble substances, such as peptones, sugars, or salts, are

absorbed in this organ, a certain amount of water must go with them, but the bulk of the water passes out of the pylorus. In the small intestine absorption of water and of inorganic salts evidently takes place readily, and according to the experiments of Röhmann and Heidenhain, already referred to, the laws governing their absorption are different from what we should expect at first sight if the process were simply one of diffusion. The differences as regards the absorption of salts are especially emphasized by the experiments of Heidenhain.<sup>1</sup> Making use of an interesting method, for which reference must be made to the original paper, Heidenhain has shown that not only dilute solutions, but solutions of nearly the same osmotic pressure as the blood were readily absorbed. Indeed, specimens of the animal's own serum introduced into a loop of the intestine were completely absorbed, although in this case there was practically no difference in composition between the liquid in the intestine and the blood of the animal. In another paper by Heidenhain<sup>2</sup> he has proved that the absorption of water in the small intestine, when ordinary amounts are ingested, takes place entirely through the blood-vessels of the villus, and not through the lacteals; when larger quantities of water are swallowed, a small part may be absorbed through the lacteals, as shown by the increased lymph-flow, but by far the larger quantity is taken up directly by the blood.

In the large intestine the contents become progressively more solid as they approach the rectum; the absorption of water is such that the stream is mainly from the intestinal contents to the blood, giving us a phenomenon somewhat similar to the absorption of water by the roots of a plant. This process is difficult to understand upon the supposition that it is caused by osmosis, using that term in its ordinary sense, unless we assume that it is due entirely to the osmotic pressure of the indiffusible proteids of the blood as explained on p. 69.

**Composition of the Feces.**—The feces differ widely in amount and in composition with the character of the food. Upon a diet composed exclusively of meats they are small in amount and dark in color; with an ordinary mixed diet the amount is increased, and it is largest with an exclusively vegetable diet, especially with vegetables containing a large amount of indigestible material. The average weight of the feces in twenty-four hours upon a mixed diet is given as 170 grams, while with a vegetable diet it may amount to as much as 400 or 500 grams. The quantitative composition, therefore, will vary greatly with the diet. Qualitatively, we find in the feces the following things: (1) Indigestible material, such as ligaments of meat or cellulose from vegetables. (2) Undigested material, such as fragments of meat, starch, or fats which have in some way escaped digestion. Naturally, the quantity of this material present is slight under normal conditions. Some fats, however, are almost always found in feces, either as neutral fats or as fatty acids, and to a small extent as calcium or magnesium soaps. The quantity of fat found is

<sup>1</sup> *Pflüger's Archiv für die gesammte Physiologie*, 1894, Bd. 56, S. 579.

<sup>2</sup> *Ibid.*, 1888, Bd. 43, supplement.



increased by an increase of the fats in the food. (3) Products of the intestinal secretions. Evidence has accumulated in recent years<sup>1</sup> to show that the feces in man on an average diet are composed mainly of the material of the intestinal secretions. The nitrogen of the feces, formerly supposed to represent undigested food, seems rather to have its origin in these secretions, and, therefore, like the nitrogen of the urine represents so much metabolism in the body. (4) Products of bacterial decomposition. The most characteristic of these products are indol and skatol. These two substances are formed normally in the large intestine from the putrefaction of proteid material. They occur always together. Indol has the formula  $C_8H_7N$ , and skatol, which is a methyl indol, the formula  $C_9H_7N$ . They are crystalline bodies possessing a disagreeable fecal odor; this is especially true of skatol, to which the odor of the feces is mainly due. Indol and skatol are eliminated from the body only in part in the feces; a certain proportion of each is absorbed into the blood and is eliminated in a modified form through the urine—indol as indican (indoxyl-sulphuric acid), from which indigo was formerly made, and skatol as skatoxyl-sulphuric acid (see Chemical section for further information as to the chemistry of these bodies). (5) Cholesterin, which is found always in small amounts and is probably derived from the bile. (6) Exeretin, a crystallizable, non-nitrogenous substance to which the formula  $C_{78}H_{156}SO_2$  has been assigned, is found in minute quantities. (7) Mucus and epithelial cells thrown off from the intestinal wall. (8) Pigment. In addition to the color due to the undigested food or to the metallic compounds contained in it, there is normally present in the feces a pigment, hydrobilirubin, derived from the pigments (bilirubin) of the bile. Hydrobilirubin is formed from the bilirubin by reduction in the large intestine. (9) Inorganic salts—salts of sodium, potassium, calcium, magnesium, and iron. The importance of the calcium and iron salts will be referred to in a subsequent chapter, when speaking of their nutritive importance. (10) Micro-organisms. Great quantities of bacteria of different kinds are found in the feces.

In addition to the feces, there is found often in the large intestine a quantity of gas that may also be eliminated through the rectum. This gas varies in composition. The following constituents have been determined to occur at one time or another:  $CH_4$ ,  $CO_2$ , H, N,  $H_2S$ . They arise mainly from the bacterial fermentation of the proteids, although some of the N may be derived from air swallowed with the food.

#### F. PHYSIOLOGY OF THE LIVER AND THE SPLEEN.

The liver plays an important part in the general nutrition of the body; its functions are manifold, but in the long run they depend upon the properties of the liver-cell, which constitutes the anatomical and physiological unit of the organ. These cells are seemingly uniform in structure throughout the whole substance of the liver, but to understand clearly the different functions they fulfil one must have a clear idea of their anatomical relations to one another

<sup>1</sup> See Prausnitz: *Zeitschrift für Biologie*, 1897, Bd. 35, S. 335; and Tauboi: *Ibid.*, S. 68.

and to the blood-vessels, the lymphatics, and the bile-ducts. The histology of the liver lobule, and the relationship of the portal vein, the hepatic artery, and the bile-duct to the lobule, must be obtained from the text-books upon histology and anatomy. It is sufficient here to recall the fact that each lobule is supplied with blood coming in part from the portal vein and in part from the hepatic artery. The blood from the former source contains the soluble products absorbed from the alimentary canal, such as sugar and proteid, and these absorbed products are submitted to the metabolic activity of the liver-cells before reaching the general circulation. The hepatic artery brings to the liver-cells the arterialized blood sent out into the systemic circulation from the left ventricle. In addition, each lobule gives origin to the bile-capillaries which arise between the separate cells and which carry off the bile formed within the cells. In accordance with these facts, the physiology of the liver-cell falls naturally into two parts—one treating of the formation, composition, and physiological significance of bile, and the other dealing with the metabolic changes produced in the mixed blood of the portal vein and the hepatic artery as it flows through the lobules. In this latter division the main phenomena to be studied are the formation of *urea* and the formation and significance of *glycogen*.

**Bile.**—From a physiological standpoint, bile is partly an excretion carrying off certain waste products, and partly a digestive secretion playing an important rôle in the absorption of fats, and possibly in other ways. Bile is a continuous secretion, but in animals possessing a gall-bladder its ejection into the duodenum is intermittent. For the details of the mechanism of its secretion, its dependence on nerve- and blood-supply, etc., the reader is referred to the section on Secretion. Bile is easily obtained from living animals by establishing a fistula of the bile-duct or, as seems preferable, of the gall-bladder. The latter operation has been performed a number of times on human beings. In some cases the entire supply of bile has been diverted in this way to the exterior, and it is an interesting physiological fact that such patients may continue to enjoy fair health, showing that, whatever part the bile takes normally in digestion and absorption, its passage into the intestine is not absolutely necessary to the nutrition of the body. The quantity of bile secreted during the day has been estimated for human beings of average weight (43 to 73 kilograms) as varying between 500 and 800 cubic centimeters. This estimate is based upon observations on cases of biliary fistula.<sup>1</sup> Chemical analyses of the bile show that, in addition to the water and salts, it contains bile-pigments, bile-acids, cholesterin, lecithin, neutral fats and soaps, sometimes a trace of urea, and a mucilaginous nucleo-albumin formerly designated improperly as *mucin*. The last-mentioned substance is not formed in the liver-cells, but is added to the bile by the mucous membrane of the bile-ducts and gall-bladder. The quantity of these substances present in the bile must vary greatly in different animals and under different conditions. As an illustration of their relative

<sup>1</sup> Copeman and Winston. *Journal of Physiology*, 1889, vol. x. p. 213; Robson: *Proceedings of the Royal Society*, London, 1890, vol. 47, p. 499; Pfaff and Balch. *Journal of Experimental Medicine*, 1897, vol. ii. p. 49.



importance in human bile and of the limits of variation the two following analyses by Hammarsten<sup>1</sup> may be quoted:

	I.	II
Solids . . . . .	2.520	2.840
Water . . . . .	97.480	97.160
Mucin and pigment . . . . .	0.529	0.910
Bile-salts . . . . .	0.931	0.814
Taurocholate . . . . .	0.3034	0.053
Glycocholate . . . . .	0.6276	0.761
Fatty acids from soap . . . . .	0.1230	0.024
Cholesterin . . . . .	0.0630	0.096
Lecithin )		
Fat        )	0.0220	0.1286
Soluble salts . . . . .	0.8070	0.8051
Insoluble salts . . . . .	0.0250	0.0411

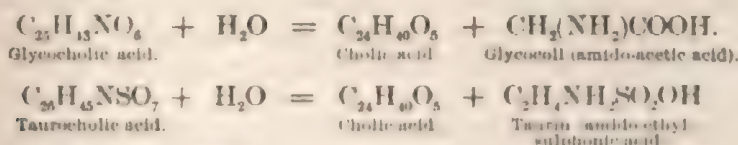
The color of bile varies in different animals according to the preponderance of one or the other of the main bile-pigments, *bilirubin* and *biliverdin*. The bile of carnivorous animals has usually a bright golden color, owing to the presence of bilirubin, while that of the herbivora is a bright green from the biliverdin. The color of human bile seems to vary: according to some authorities, it is yellow or brownish yellow, and this seems especially true of the bile as found in the gall-bladder of the cadaver; according to others, it is of a dark-olive color with the greenish tint predominating. Its reaction is feebly alkaline, and its specific gravity varies in human bile from 1050 or 1040 to 1010. Human bile does not give a distinctive absorption spectrum, but the bile of some herbivora, after exposure to the air at least, gives a characteristic spectrum. The individual constituents of the bile will now be described more in detail, but with reference mainly to their origin, fate, and function in the body. For a description of their strictly chemical properties and reactions reference must be made to the Chemical section.

**Bile-pigments.**—Bile, according to the animal from which it is obtained, contains one or the other, or a mixture, of the two pigments *bilirubin* and *biliverdin*. Biliverdin is supposed to stand to bilirubin in the relation of an oxidation product. Bilirubin is given the formula  $C_{16}H_{18}N_2O_6$ , and biliverdin  $C_{16}H_{18}N_2O_7$ , the latter being prepared readily from pure specimens of the former by oxidation. These pigments give a characteristic reaction, known as "Gmelin's reaction," with nitric acid containing some nitrous acid (nitric acid with a yellow color). If a drop of bile and a drop of nitric acid are brought into contact, the former undergoes a succession of color changes, the order being green, blue, violet, red, and reddish yellow. The play of colors is due to successive oxidations of the bile-pigments; starting with bilirubin, the first stage (green) is due to the formation of biliverdin. The pigments formed in some of the other stages have been isolated and named. The reaction is very delicate, and it is often used to detect the presence of bile-pigments in other liquids—urine, for example. The bile-pigments originate

<sup>1</sup> Reported in *Centralblatt für Physiologie*, 1894, No. 8.

from hæmoglobin. This origin was first indicated by the fact that in old blood-clots or in extravasations there was found a crystalline product, the so-called "hæmatoidin," which was undoubtedly derived from hæmoglobin, and which upon more careful examination was proved to be identical with bilirubin. This origin, which has since been made probable by other reactions, is now universally accepted. It is supposed that when the blood-corpuscles go to pieces in the circulation (p. 45) the hæmoglobin is brought to the liver, and then, under the influence of the liver-cells, is converted to an iron-free compound, bilirubin or biliverdin. It is very significant to find that the iron separated by this means from the hæmoglobin is for the most part retained in the liver, a small portion only being secreted in the bile. It seems probable that the iron held back in the liver is again used in some way to make new hæmoglobin in the hæmatopoietic organs. The bile-pigments are carried in the bile to the duodenum and are mixed with the food in its long passage through the intestine. Under normal conditions neither bilirubin nor biliverdin is found in the feces, but in their place is found a reduction product, *hydrobilirubin*, formed in the large intestine. Moreover, it is believed that some of the bile-pigment is reabsorbed as it passes along the intestine, is carried to the liver in the portal blood, and is again eliminated. That this action occurs, or may occur, has been made probable by experiments of Wertheimer<sup>1</sup> on dogs. It happens that sheep's bile contains a pigment (cholo-hæmatin) that gives a characteristic spectrum. If some of this pigment is injected into the mesenteric veins of a dog, it is eliminated while passing through the liver, and can be recognized unchanged in the bile. The value of this "circulation of the bile," so far as the pigments are concerned, is not apparent.

**Bile-acids.**—"Bile-acids" is the name given to two organic acids, *glycocholic* and *taurocholic*, which are always present in bile, and, indeed, form very important constituents of that secretion; they occur in the form of their respective sodium salts. In human bile both acids are usually found, but the proportion of taurocholate is variable, and in some cases this latter acid may be absent altogether. Among herbivora the glycocholate predominates as a rule, although there are some exceptions; among the carnivora, on the other hand, taurocholate occurs usually in greater quantities, and in the dog's bile it is present alone. Glycocholic acid has the formula  $C_{25}H_{43}NO_6$ , and taurocholic acid has the formula  $C_{26}H_{45}NSO_7$ . Each of them can be obtained in the form of crystals. When boiled with acids or alkalis these acids take up water and undergo hydrolytic cleavage, the reaction being represented by the following equations:



<sup>1</sup> *Archives de Physiologie normale et pathologique*, 1892, p. 577.



These reactions are interesting not only in that they throw light on the structure of the acids, but also because similar reactions doubtless take place in the intestine, cholic acid having been detected in the intestinal contents. As the formulas show, cholic acid is formed in the decomposition of each acid, and we may regard the bile-acids as compounds produced by the synthetic union of cholic acid with glycocholic in the one case and with taurin in the other. Cholic acid or its compounds, the bile-acids, are usually detected in suspected liquids by the well-known Pettenkofer reaction. As usually performed, the test is made by adding to the liquid a few drops of a 10 per cent. solution of cane-sugar and then strong sulphuric acid. The latter must be added carefully and the temperature be kept below  $70^{\circ}\text{C}$ . If bile-acids are present, the liquid assumes a beautiful red-violet color. It is now known that the reaction consists in the formation of a substance (furfural) by the action of the acid on sugar, which then reacts with the bile-acids. The bile-acids are formed directly in the liver-cells. This fact, which was for a long time the subject of discussion, has been demonstrated in recent years by an important series of researches made upon birds. It has been shown that if the bile-duct is ligated in these animals, the bile formed is reabsorbed and bile-acids and pigments may be detected in the urine and the blood. If, however, the liver is completely extirpated, then no trace of either bile-acids or bile-pigments can be found in the blood or the urine, showing that these substances are not formed elsewhere in the body than in the liver. It is more difficult to ascertain from what substances they are formed. The fact that glycocholic and taurin contain nitrogen, and that the latter contains sulphur, indicates that some proteid or albuminoid constituent is broken down during their production.

A circumstance of considerable physiological significance is that these acids or their decomposition products are absorbed in part from the intestine and are again secreted by the liver: as in the case of the pigments, there is an intestinal-hepatic circulation. The value of this reabsorption may lie in the fact that the bile-acids constitute a very efficient stimulus to the bile-secreting activity of the cells, being one of the best of cholagogues, or it may be that it economizes material. From what we know of the history of the bile-acids it is evident that they are not to be considered as excreta: they have some important function to fulfil. The following suggestions as to their value have been made: In the first place, they serve as a menstruum for dissolving the cholesterin which is constantly present in the bile and which is an excretion to be removed; secondly, they facilitate the absorption of fats from the intestine. The value of bile in fat-absorption will presently be referred to more in detail. It is an undoubted fact that when bile is shut off from the intestine the absorption of fats is very much diminished, and it has been shown that this action of the bile in fat absorption is owing to the presence of the bile-acids.

**Cholesterin.**—Cholesterin is a non-nitrogenous substance of the formula  $\text{C}_{20}\text{H}_{44}\text{O}$  or  $\text{C}_{27}\text{H}_{45}(\text{OH})$ . It is a constant constituent of the bile, although it

occurs in variable quantities. Cholesterin is very widely distributed in the body, being found especially in the white matter (medullary substance) of nerve-fibres. It seems, moreover, to be a constant constituent of all animal and plant cells. It is assumed that cholesterin is not formed in the liver, but that it is eliminated by the liver-cells from the blood, which collects it from the various tissues of the body. That it is an excretion is indicated by the fact that it is eliminated unchanged in the feces. Cholesterin is insoluble in water or in dilute saline liquids, and is held in solution in the bile by means of the bile-acids. We must regard it as a waste product of cell-life, formed probably in minute quantities, and excreted mainly through the liver. It is partly eliminated through the skin, in the sebaceous and sweat secretions, and in the milk.

**Lecithin, Fats, and Nucleo-albumin.**—*Lecithin* also seems to be present, generally in small quantities, in the cells of the various tissues, but it occurs especially in the white matter of nerve-fibres. It is probable, therefore, that, so far as it is found in the bile, it represents a waste product formed in different parts of the body and eliminated through the bile. The special importance, if any, of the small proportion of fats and fatty acids in the bile is unknown. The ropy, mucilaginous character of bile is due to the presence of a body formed in the bile-ducts and gall-bladder. This substance was formerly designated as *mucin*, but it is now known that in ox-bile at least it is not a true mucin, but is a *nucleo-albumin* (see Chemical section). Hammarsten reports that in human bile some true mucin is found. Outside the fact that it makes the bile viscous, this constituent is not known to possess any especial physiological significance.

**General Physiological Importance of Bile.**—The physiological value of bile has been referred to in speaking of its several constituents, but it will be convenient here to restate these facts and to add a few remarks of general interest. Bile is of importance as an excretion in that it removes from the body waste products of metabolism, such as cholesterin, lecithin, and bile-pigments. With reference to the pigments, there is evidence to show that a part at least may be reabsorbed while passing through the intestine, and be used again in some way in the body. The bile-acids represent end-products of metabolism involving the proteids of the liver-cells, but they are undoubtedly reabsorbed in part, and cannot be regarded merely as excreta. As a digestive secretion the most important function attributed to the bile is the part it takes in the digestion of fats. In the first place, it aids in the splitting of a part of the neutral fats and the subsequent emulsification of the remainder (p. 307). More than this, bile aids materially in the absorption of the digested fats. A number of observers have shown that when a permanent biliary fistula is made, and the bile is thus prevented from reaching the intestinal canal, a large proportion of the fat of the food escapes absorption and is found in the feces. This property of the bile is known to depend upon the bile-acids it contains, but how they act is not clearly understood. It was formerly believed, on the basis of some experiments by von Westinghausen,



that the bile-acids dissolve or mix with the fats and at the same time moisten the mucous membrane, and for these reasons aid in bringing the fat into immediate contact with the epithelial cells. It was stated, for instance, that oil rises higher in capillary tubes moistened with bile than in similar tubes moistened with water, and that oil will filter more readily through paper moistened with bile than through paper wet with water. Gröper,<sup>1</sup> who repeated these experiments, finds that they are erroneous. It seems certain, however, that the bile-acids enable the bile to hold in solution a considerable quantity of fatty acids, and possibly this fact explains its connection with fat absorption. It was formerly believed that bile is also of great importance in restraining the processes of putrefaction in the intestine. It was asserted that bile is an efficient antiseptic, and that this property comes into use normally in preventing excessive putrefaction. Bacteriological experiments made by a number of observers have shown, however, that bile itself has very feeble antiseptic properties, as is indicated by the fact that it putrefies readily. The free bile-acids and cholalic acid do have a direct retarding effect upon putrefactions outside the body; but this action is not very pronounced, and has not been demonstrated satisfactorily for bile itself. It seems to be generally true that in cases of biliary fistula the feces have a very fetid odor when meat and fat are taken in the food. But the increased putrefaction in these cases may possibly be due to some indirect result of the withdrawal of bile. It has been suggested, for instance, that the deficient absorption of fat that follows upon the removal of the bile results in the proteid and carbohydrate material becoming coated with an insoluble layer of fat, so that the penetration of the digestive enzymes is retarded and greater opportunity is given for the action of bacteria. We may conclude, therefore, that while there does not seem to be sufficient warrant at present for believing that the bile exerts a direct antiseptic action upon the intestinal contents, nevertheless its presence limits in some way the extent of putrefaction. Lastly, bile takes a direct part in suspending or destroying peptic digestion in the acid chyme forced from the stomach into the duodenum. The chyme meeting with bile and pancreatic juice is neutralized or is made alkaline, which alone would prevent further peptonization. Moreover, when chyme and bile are mixed a precipitate occurs, consisting partly of proteids (proteoses and syntonin) and partly of bile-acids. It is probable that pepsin, according to its well-known property, is thrown down in this flocculent precipitate and, as it were, prepared for its destruction.

**Glycogen.**—One of the most important functions of the liver is the formation of *glycogen*. This substance was found in the liver in 1857 by Claude Bernard, and is one of several brilliant discoveries made by him. Glycogen has the formula  $(C_6H_{10}O_5)_n$ , which is also the general formula given to vegetable starch; glycogen is therefore frequently spoken of as "animal starch." It gives, however, a port-wine-red color with iodine solutions, instead of the familiar deep blue of vegetable starch, and this reaction serves to detect glyco-

<sup>1</sup> *Archiv für Anatomie und Physiologie* ("Physiol. Abtheilung"), 1889, S. 505.

gen not only in its solutions, but also in the liver-cells. Glycogen is readily soluble in water, and the solutions have a characteristic opalescent appearance. Like starch, glycogen is acted upon by ptyalin and amylase, and the end-products are apparently the same—namely, maltose, or maltose and some dextrin. For a more complete account of the chemical relations of glycogen reference must be made to the Chemical section.

**Occurrence of Glycogen in the Liver.**—Glycogen can be detected in the liver-cells microscopically. If the liver of a dog is removed twelve or fourteen hours after a hearty meal, hardened in alcohol, and sectioned, the liver-cells will be found to contain clumps of clear material which give the iodine reaction for glycogen. Even when distinct aggregations of the glycogen cannot be made out, its presence in the cells is shown by the red reaction with iodine. By this simple method one can demonstrate the important fact that the amount of glycogen in the liver increases after meals and decreases again during the fasting hours, and if the fast is sufficiently prolonged it may disappear altogether. This fact is, however, shown more satisfactorily by quantitative determinations, by chemical means, of the total glycogen present. The amount of glycogen present in the liver is quite variable, being influenced by such conditions as the character and amount of the food, muscular exercise, body-temperature, drugs, etc. From determinations made upon various animals it may be said that the average amount lies between 1.5 and 4 per cent. of the weight of the liver. But this amount may be increased greatly by feeding upon a diet largely made up of carbohydrates. It is said that in the dog the total amount of liver-glycogen may be raised to 17 per cent., and in the rabbit to 27 per cent., by this means, while it is estimated for man (Neumeister) that the quantity may be increased to at least 10 per cent. It is usually believed that glycogen exists as such in the liver-cells, being deposited in the substance of the cytoplasm. Reasons have been brought forward recently to show that possibly this is not strictly true, but that the glycogen is held in some sort of weak chemical combination. It has been shown, for instance, that although glycogen is easily soluble in cold water, it cannot be extracted readily from the liver-cells by this agent. One must use hot water, salts of the heavy metals, and other similar means that may be supposed to break up the combination in which the glycogen exists. For practical purposes, however, we may speak of the glycogen as lying free in the liver-cells, just as we speak of hemoglobin existing as such in the red corpuscles, although it is probably held in some sort of combination.

**Origin of Glycogen.**—To understand clearly the views held as to the origin of liver glycogen, it will be necessary to describe briefly the effect of the different food-stuffs upon its formation.

**Effect of Carbohydrates on the Amount of Glycogen.**—The amount of glycogen in the liver is affected very quickly by the quantity of carbohydrates in the food. If the carbohydrates are given in excess, the supply of glycogen may be increased largely beyond the average amount present, as has been stated above. Investigation of the different sugars has shown that dextrose, levulose,



saccharose (cane-sugar), and maltose are unquestionably direct glycogen-formers, that is, that glycogen is formed directly from them or from the products into which they are converted during digestion. Now, our studies in digestion have shown that the starches are converted into maltose, or maltose and dextrin, during digestion, and, further, that these substances are changed or inverted to the simpler sugar dextrose during absorption. Cane-sugar, which forms such an important part of our diet, is inverted in the intestine into dextrose and levulose, and is absorbed in these forms. It is evident, therefore, that the bulk of our carbohydrate food reaches the liver as dextrose, or as dextrose and levulose, and these forms of sugar must be converted into glycogen in the liver-cells by a process of dehydration such as may be represented in substance by the formula  $C_6H_{12}O_6 - H_2O = C_6H_{10}O_5$ . There is no doubt that both dextrose and levulose increase markedly the amount of glycogen in the liver; and, since cane-sugar is inverted in the intestine before absorption, it also must be a good glycogen-former—a fact that has been abundantly demonstrated by direct experiment. Lusk<sup>1</sup> has shown, however, that if cane-sugar is injected under the skin, it has a very feeble effect in the way of increasing the amount of glycogen in the liver, since under these conditions it is probably absorbed into the blood without undergoing inversion. Experiments with subcutaneous injection of lactose gave similar results, and it is generally believed that the liver-cells cannot convert the double sugars to glycogen, at least not readily; hence the value of the hydrolysis of these sugars in the alimentary canal before absorption. The relations of lactose to glycogen-formation have not been determined satisfactorily. If it contributes at all to the direct formation of glycogen, it is certainly less efficient than dextrose, levulose, or cane-sugar. When the proportion of lactose in the diet is much increased, it quickly begins to appear in the urine, showing that the limit of its consumption in the body is soon reached. This latter fact is somewhat singular, since in infancy especially milk-sugar forms a constant and important item of our diet, and one would suppose that it is especially adapted to the needs of the body.

*Effect of Proteids on Glycogen-formation.*—It was pointed out by Bernard, in his first studies upon glycogen-formation, that the liver can produce glycogen from proteid food. This conclusion has since been verified by more exact investigations. When an animal is fed upon a diet of proteid alone, or on proteid and gelatin, the carbohydrates being entirely excluded, glycogen is still formed in the liver, although in smaller amounts than in the case of carbohydrate foods. This is an important fact to remember in studying the metabolism of the proteids in the body, for, as glycogen is a carbohydrate and contains no nitrogen, it implies that the proteid molecule is dissociated into a nitrogenous and a non-nitrogenous part, the latter being converted to glycogen by the liver-cells. The possibility of the production of glycogen from proteids accords with a well-known fact in medical practice with reference to the pathological condition known as *diabetes*. In this disease sugar is excreted in the urine, sometimes in large quantities. As the sugar of the blood is believed

<sup>1</sup> Voit: *Zeitschrift für Biologie*, 1891, xxviii. S. 285.

to be formed ordinarily from the carbohydrates in the food, it was thought that by excluding this food-stuff from the diet the excretion of sugar might be prevented. It has been found, however, that in severe cases at least sugar continues to be present in the urine even upon a pure proteid diet. If we suppose that some of the proteid goes to form glycogen, the result observed is explained, for the glycogen, as will be explained presently, is finally converted to sugar and is given off to the blood. An interesting additional fact that points to the same conclusion is that the percentage of sugar in the blood remains practically constant after prolonged starvation, at a time when the animal is living at the expense of the proteids and fats of its own body.

*Effect of Fats and other Substances upon Glycogen-formation.*—It has been found that fats take no part in the formation of liver glycogen. Some attempts have been made to prove that fat in the body, and particularly in the liver, may be converted to sugar, but the evidence at present seems to be against this possibility.<sup>1</sup>

**The Function of Glycogen : Glycogenic Theory.**—The meaning of the formation of glycogen in the liver has been, and still is, the subject of discussion. The view advanced first by Bernard is perhaps most generally accepted. According to Bernard, glycogen forms a temporary reserve supply of carbohydrate material that is laid up in the liver during digestion and is gradually made use of in the intervals between meals. During digestion the carbohydrate food is absorbed into the blood of the portal system as dextrose or as dextrose and levulose. If these passed through the liver unchanged, the contents of the systemic blood in sugar would be increased perceptibly. It is now known that when the percentage of sugar in the blood rises above a certain low limit, the excess will be excreted through the kidney and will be lost. But as the blood from the digestive organs passes through the liver the excess of sugar is abstracted from the blood by the liver-cells, is dehydrated to make glycogen, and is retained in the cells in this form for a short period. From time to time the glycogen is reconverted into sugar (dextrose) and is given off to the blood. By this means the percentage of sugar in the systemic blood is kept nearly constant (0.1 to 0.2 per cent.) and within limits best adapted for the use of the tissues. The great importance of the formation of glycogen and the consequent conservation of the sugar-supply of the tissues will be more evident when we come to consider the nutritive value of carbohydrate food. Carbohydrates form the bulk of our usual diet, and the proper regulation of the supply to the tissues is therefore of vital importance in the maintenance of a normal healthy condition. The second part of this theory, which holds that the glycogen is reconverted to dextrose, is supported by observations upon livers removed from the body. It has been found that shortly after the removal of the liver the supply of glycogen begins to disappear and a corresponding increase in dextrose occurs. Within a comparatively short time all the glycogen is gone and only dextrose is found. It is for this reason that in

<sup>1</sup> Kumagawa and Minra: *Archiv für Anatomie und Physiologie* ("Physiol. Abtheilung"), 1898, S. 431, contains also reference to the literature of the subject.



the estimation of glycogen in the liver it is necessary to mince the organ and to throw it into boiling water as quickly as possible, since by this means the liver-cells are killed and the conversion of the glycogen is stopped. How the glycogen is changed to dextrose by the liver is a matter not fully explained. According to some authors, the conversion is due to an enzyme produced in the liver. Extracts of liver, as of some other tissues, do yield an amylolytic enzyme that changes glycogen to dextrose.<sup>1</sup> It is possible, therefore, that the conversion of glycogen to dextrose is effected by a special enzyme produced in the liver-cells. In this description of the origin and meaning of the liver glycogen reference has been made only to the glycogen derived directly from digested carbohydrates. The glycogen derived from proteid foods, once it is formed in the liver, has, of course, the same functions to fulfil. It is converted into sugar, and eventually is oxidized in the tissues. For the sake of completeness it may be well to add that some of the sugar of the blood formed from the glycogen may under certain conditions be converted into fat in the adipose tissues, instead of being burnt, and in this way it may be retained in the body as a reserve supply of food of a more stable character than is the glycogen.

**Glycogen in the Muscles and other Tissues.**—The history of glycogen is not complete without some reference to its occurrence in the muscles. Glycogen is, in fact, found in various places in the body, and is widely distributed throughout the animal kingdom. It occurs, for example, in leucocytes, in the placenta, in the rapidly-growing tissues of the embryo, and in considerable abundance in the oyster and other molluscs. But in our bodies and in those of the mammals generally the most significant occurrence of glycogen, outside the liver, is in the voluntary muscles, of which glycogen forms a normal constituent. It has been estimated that the percentage of glycogen in resting muscle varies from 0.5 to 0.9 per cent., and that in the musculature of the whole body there may be contained an amount of glycogen equal to that in the liver itself. Apparently muscular tissue, as well as liver-tissue, has a glycogenetic function—that is, it is capable of laying up a supply of glycogen from the sugar brought to it by the blood. The glycogenetic function of muscle has been demonstrated directly by Kulz,<sup>2</sup> who has shown that an isolated muscle irrigated with an artificial supply of blood to which dextrose had been added is capable of changing the dextrose to glycogen, as shown by the increase in the latter substance in the muscle after irrigation. Muscle glycogen is to be looked upon, probably, for reasons to be mentioned in the next paragraph, as a temporary and local reserve supply of material, so that, while we have in the liver a large general depot for the temporary storage of glycogen for the use of the body at large, the muscular tissue, which is the most active tissue of the body from a chemical standpoint, is also capable of laying up in the form of glycogen any excess of sugar brought to it. The fact that glycogen occurs so widely in the rapidly-growing tissues of embryos indicates that this glycogenetic function may at times be exercised by any tissue.

<sup>1</sup> Tabl.: *Journal of Physiology*, 1897-98, vol. xxii, p. 423.

<sup>2</sup> *Zeitschrift für Biologie*, 1890, 8, 237.

**Conditions Affecting the Supply of Glycogen in Muscle and Liver.—**

In accordance with the view given above of the general value of glycogen—namely, that it is a temporary reserve supply of carbohydrate material that may be rapidly converted to sugar and oxidized with the liberation of energy—it is found that the supply of glycogen is greatly affected by conditions calling for increased metabolism in the body. Muscular exercise will quickly exhaust the supply of muscle and liver glycogen, provided it is not renewed by new food. In a starving animal glycogen will finally disappear, except perhaps in traces, but this disappearance will occur much sooner if the animal is made to use its muscles at the same time. It has been shown also by Morat and Dufourt that if a muscle has been made to contract vigorously, it will take up much more sugar from an artificial supply of blood sent through it than a similar muscle which has been resting; on the other hand, it has been found that if the nerve of one leg is cut so as to paralyze the muscles of that side of the body, the amount of glycogen will increase rapidly in these muscles as compared with those of the other leg, that have been contracting meantime and using up their glycogen.

**Formation of Urea in the Liver.**—The nitrogen contained in the proteid material of our food is finally eliminated, after the metabolism of the proteid is completed, mainly in the form of urea. As will be explained in another part of this section, it has been definitively proved that the urea is not formed in the kidneys, the organs that eliminate it. It has long been considered a matter of the greatest importance to ascertain in what organ or tissues urea is formed. Investigations have gone so far as to demonstrate that it arises in part at least in the liver; hence the property of forming urea must be added to the other important functions of the liver-cell. Schröder<sup>1</sup> performed a number of experiments in which the liver was taken from a freshly-killed dog and irrigated through its blood-vessels by a supply of blood obtained from another dog. If the supply of blood was taken from a fasting animal, then circulating it through the isolated liver was not accompanied by any increase in the amount of urea contained in it. If, on the contrary, the blood was obtained from a well-fed dog, the amount of urea contained in it was distinctly increased by passing it through the liver, thus indicating that the blood of an animal after digestion contains something that the liver can convert to urea. It is to be noted, moreover, that this power is not possessed by all the organs, since blood from well-fed animals showed no increase in urea after being circulated through an isolated kidney or muscle. As further proof of the urea-forming power of the liver Schröder found that if ammonium carbonate was added to the blood circulating through the liver—to that from the fasting as well as from the well-nourished animal—a very decided increase in the urea always followed. It follows from the last experiment that the liver-cells are able to convert carbonate of ammonium into urea. The reaction may be expressed by the equation  $(\text{NH}_4)_2\text{CO}_3 - 2\text{H}_2\text{O} = \text{CON}_2\text{H}_4$ . Schöndorff<sup>2</sup> in some later work showed that if the blood of a fasting dog is irrigated through

<sup>1</sup> *Archiv für experimentelle Pathologie und Pharmacologie*, Bde. xv. and xix., 1882 and 1885.

<sup>2</sup> *Pflüger's Archiv für die gesammte Physiologie*, 1893, Bd. liv. S. 420.



the hind legs of a well-nourished animal, no increase in urea in the blood can be detected; but if the blood, after irrigation through the hind legs, is subsequently passed through the liver, a marked increase in urea results. Obviously, the blood in this experiment derives something from the tissues of the leg which the tissues themselves cannot convert to urea, but which the liver-cells can. Finally, in some remarkable experiments upon dogs made by four investigators (Hahn, Massen, Nencki, and Pawlow), which will be described briefly in the next section in connection with urea, it was shown that when the liver is practically destroyed there is a distinct diminution in the urea of the urine. In birds uric acid takes the place of urea as the main nitrogenous excretion of the body, and Minkowski has shown that in them removal of the liver is followed by an important diminution in the amount of uric acid excreted. From experiments such as these it is safe to conclude that urea is formed in the liver and is then given to the blood and excreted by the kidney. When we come to describe the physiological history of urea (p. 334), an account will be given of the views held with regard to the antecedent substance or substances from which the liver produces urea.

**Physiology of the Spleen.**—Much has been said and written about the spleen, but we are yet in the dark as to the distinctive function or functions of this organ. The few facts that are known may be stated briefly without going into the details of theories that have been offered at one time or another. The older experimenters demonstrated that this organ may be removed from the body without serious injury to the animal. An increase in the size of the lymph-glands and of the bone-marrow has been stated to occur after extirpation; but this is denied by others, and, whether true or not, it gives but little clue to the normal functions of the spleen. Laudenbach<sup>1</sup> finds that one result of the removal of the spleen is a marked diminution in the number of red corpuscles and the quantity of hæmoglobin. He infers, therefore, that the spleen is normally concerned in some way in the formation of red corpuscles. These facts are significant, but they need, perhaps, further confirmation. The most definite facts known about the spleen are in connection with its movements. It has been shown that there is a slow expansion and contraction of the organ synchronous with the digestion periods. After a meal the spleen begins to increase in size, reaching a maximum at about the fifth hour, and then slowly returns to its previous size. This movement, the meaning of which is not known, is probably due to a slow vaso-dilatation, together, perhaps, with a relaxation of the tonic contraction of the musculature of the trabecule. In addition to this slow movement, Roy<sup>2</sup> has shown that there is a rhythmic contraction and relaxation of the organ, occurring in cats and dogs at intervals of about one minute. Roy supposes that these contractions are effected through the intrinsic musculature of the organ—that is, the plain muscle-tissue present in the capsule and trabecule—and he believes that the contractions serve to keep up a circulation through the spleen and to make its vascular supply more

<sup>1</sup> *Centralblatt für Physiologie*, 1895, Bd. ix, S. 1.

<sup>2</sup> *Journal of Physiology*, 1881, vol. iii, p. 203.

or less independent of variations in general arterial pressure. These observations are valuable as indicating the importance of the spleen functions. The fact that there is a special local arrangement for maintaining its circulation makes the spleen unique among the organs of the body, but no light is thrown upon the nature of the function fulfilled. The spleen is supplied richly with nerve-fibres which when stimulated either directly or reflexly cause the organ to diminish in volume. According to Schaefer,<sup>1</sup> these fibres are contained in the splanchnic nerves, which carry also inhibitory fibres whose stimulation produces a dilatation of the spleen.

The chemical composition of the spleen is complicated but suggestive. Its mineral constituents are characterized by a large percentage of iron, which seems to be present as an organic compound of some kind. Analysis shows also the presence of a number of fatty acids, fats, cholesterin, and, what is perhaps more noteworthy, a number of nitrogenous extractives such as xanthin, hypoxanthin, adenin, guanin, and uric acid. The presence of these bodies seems to indicate that active metabolic changes of some kind occur in the spleen. As to the theories of the splenic functions, the following may be mentioned: (1) The spleen has been supposed to give rise to new red corpuscles. This it undoubtedly does during fetal life and shortly after birth, and in some animals throughout life, but there is no reliable evidence that the function is retained in adult life in man or in most of the mammals. (2) It has been supposed to be an organ for the destruction of red corpuscles. This view is founded partly on very unsatisfactory microscopic evidence according to which certain large ameboid cells in the spleen ingest and destroy the old red corpuscles, and partly upon the fact that the spleen-tissue seems to be rich in an iron-containing compound. This theory cannot be considered at present as anything more than a suggestion. (3) It has been suggested that uric acid is produced in the spleen. This substance is found in the spleen, as stated above, and it has been shown by Horbacewsky that the spleen contains a substance from which uric acid or xanthin may readily be formed; but further investigation has shown that the same substance is found in lymphoid tissue generally. If, therefore, uric acid is produced in the spleen, it is a function of the large amount of lymphoid tissue contained in it, and a function which it shares with similar tissues in the rest of the body. The lymphoid tissue of the spleen must also possess the property of producing lymphocytes, since, according to the general view, these corpuscles are formed in lymphoid tissue generally wherever the so-called "germ-centres" occur. (4) Lastly, a theory has been supported by Schiff and Herzen, according to which the spleen produces something (an enzyme) which, when carried in the blood to the pancreas, acts upon the trypsinogen contained in this gland, converting it into trypsin. The experimental evidence upon which this view rests has not been confirmed by other observers.

<sup>1</sup> *Proceedings of the Royal Society, London*, 1896, vol. lix., No. 355, and *Journal of Physiology*, 1896, vol. xx.



## G. THE KIDNEY AND THE SKIN AS EXCRETORY ORGANS.

The secretion of the kidneys is the *urine*. The means by which this secretion is produced, its relations to the histological structure of the kidney, and its connections with the blood- and nerve-supply of that organ will be found described in the section on Secretion. In this section will be discussed only the chemical composition of urine, and especially the physiological significance of its different constituents. The urine of man is a yellowish liquid varying greatly in depth of color. It has an average specific gravity of 1020, and an acid reaction. The acid reaction is not due to a free acid, but is usually attributed to an acid salt, the acid phosphate of sodium ( $\text{NaH}_2\text{PO}_4$ ). Under certain normal conditions human urine may show a neutral or even a slightly alkaline reaction, especially after meals. In fact, the reaction of the urine seems to depend directly on the character of the food. Among carnivorous animals the urine is uniformly acid, and among herbivorous animals it is uniformly alkaline, so long as they are using a vegetable diet, but when starving or when living upon the mother's milk—that is, whenever they are existing upon a purely animal diet—the urine becomes acid. The explanation, as given by Dreesel, is that upon an animal diet more acids are produced (from the sulphur and phosphorus) than the bases present can neutralize, whereas upon a vegetable diet carbonates are formed from the oxidation of the organic acids of the food in quantities sufficient to neutralize the mineral acids. The chemical composition of urine is very complex. Among the constituents constantly present under the conditions of normal life we have, in addition to water and inorganic salts, the following substances: Urea; uric acid; xanthin; creatinin; hippuric acid; the urinary pigments (urobilin); sulphocyanides in traces; acetone; oxalic acid, probably as calcium oxalate; several ethereal sulphuric acids, such as phenol and cresol sulphuric acids, indoxyl sulphuric acid (indican), and skatoxyl sulphuric acid; aromatic oxy-acids; some combinations of glycuronic acid; some representatives of the fatty acids; and dissolved gases ( $\text{N}$  and  $\text{CO}_2$ ). This list would be very much extended if it attempted to take in all those substances occasionally found in the urine. The complexity of the composition and the fact that so many different organic compounds occur or may occur in small quantities is readily understood when we consider the nature of the secretion. Through the kidneys there are eliminated not only what we might call the normal end-products of the metabolism of the tissues, excluding the  $\text{CO}_2$ , but also, in large part, the products of decomposition in the alimentary canal, the end-products of many organic substances occurring in our foods and not usually classed as food-stuffs, foreign substances introduced as drugs, etc., all of which are eliminated either in the form in which they are taken or as derivative products of some kind. We shall speak briefly of the most important of the normal constituents, dwelling especially upon their origin in the body and their physiological significance. For details of chemical properties and reactions, reference must be made to the Chemical section.

**Urea.**—Urea, which is given the formula  $\text{CH}_4\text{N}_2\text{O}$ , is usually considered

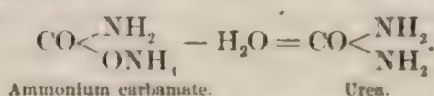
as an amide of carbonic acid, having therefore the structural formula of  $\text{CO} < \begin{smallmatrix} \text{NH}_2 \\ \text{NH}_2 \end{smallmatrix}$ . It occurs in the urine in relatively large quantities (2 per cent. +).

As the total quantity of urine secreted in twenty-four hours by an adult male may be placed at from 1500 to 1700 cubic centimeters, it follows that from 30 to 34 grams of urea are eliminated from the body during this period. It is the most important of the nitrogenous excreta of the body, the end-product of the physiological oxidation of the proteids of the body, and also of the albuminoids when they appear in the food. If we know how much urea is secreted in a given period, we know approximately how much proteid has been broken down in the body in the same time. In round numbers, 1 gram of proteid will yield  $\frac{1}{3}$  gram of urea, as may be calculated easily from the amount of nitrogen contained in each. Since, however, some of the nitrogen of proteid is eliminated in other forms—uric acid, creatinin, etc.—even an exact determination of all the urea would not be sufficient to determine with accuracy the total amount of proteid broken down. This fact is arrived at more perfectly, as we shall explain later, by a determination of the total nitrogen of the urine and other excretions. In addition to the urine, urea is found in slight quantities in other secretions, in milk (in traces), and in sweat. In the latter liquid the quantity of urea in twenty-four hours may be quite appreciable—as much, for instance, as 0.8 gram—although such a large amount is found only after active exercise. It has been ascertained definitely that urea is not formed by the kidneys: it is brought to the kidneys in the blood for elimination, the cells of the convoluted tubules being especially adapted for taking up this material and transmitting it through their substance to the lumen of the tubules. That urea is not made in the kidneys is demonstrated by such facts as these: If blood, on the one hand, is irrigated through an isolated kidney, no urea is formed, even though substances (such as ammonium carbonate) from which urea is readily produced are added to the blood; on the other hand, urea is constantly present in the blood (0.0348 to 0.1529 per cent.), and if the two kidneys are removed, it continues to accumulate steadily in the blood as long as the animal survives. It has been ascertained that the urea is produced in part in the liver; an account of some of the experiments demonstrating this fact is given on page 331. The most important questions that remain to be decided are, Through what steps is the proteid molecule metabolized to the form of urea? and, What is the antecedent substance brought to the liver, from which it makes urea? It is impossible to answer these questions perfectly, but recent investigations have thrown a great deal of light on the whole process, and they give hope that before long the entire history of the derivation of urea from proteids and albuminoids will be known. The results of this work may be stated briefly as follows:

1. Urea arises from proteids by a process of hydrolysis and oxidation, with the formation eventually of ammonia compounds, which are then conveyed to the liver and there changed to urea. Drechsel has suggested that ammonium carbamate forms one at least of the ammonia compounds that are con-



verted to urea, and gives the following evidence for this view. In the first place, Drechsel found carbamic acid in the blood of dogs, and Drechsel and Abel have shown that it occurs normally in the urine of horses as calcium carbamate; and Abel has shown that it may be found in the urine of dogs or infants after the use of lime-water. Drechsel has shown, further, that ammonium carbamate may be converted into urea. If one compares the formulas of ammonium carbamate and urea, it is seen that the former may pass over into the latter by the loss of a molecule of water, as—



Drechsel supposes, however, that this dehydration is effected in an indirect manner; that there is first an oxidation removing two atoms of hydrogen, and then a reduction removing an atom of oxygen. He succeeded in showing that when an aqueous solution of ammonium carbamate is submitted to electrolysis, and the direction of the current is changed repeatedly so as to get alternately reduction and oxidation processes at each pole, some urea will be produced. These facts show the existence of ammonium carbamate in the body, and the possibility of its conversion to urea. It remains possible, however, that other salts or compounds of ammonia may likewise be converted normally to urea by the liver, since it has been shown experimentally in artificial circulation through this organ that salts such as ammonium carbonate, or even such complex ammonia compounds as leucin and glycocoll, may give rise to urea. Experiments made by Hahn, Pawlow, Massen, and Nencki<sup>1</sup> show that in dogs removal of the liver is followed by a decrease in the amount of urea in the urine and an increase in the ammonia contents. In these remarkable experiments a fistula was made between the portal vein and the inferior vena cava, the result of which was that the whole portal circulation of the liver was abolished, and the only blood that the organ received was through the hepatic artery. If, now, this artery was ligated or the liver was cut away, as was done in some of the experiments, then the result was practically an extirpation of the entire organ—an operation which has always been thought to be impossible with mammals. The animals in these investigations survived this operation for some time, but they died finally, showing a series of symptoms which indicated a deep disturbance of the nervous system. It was found that the symptoms of poisoning in these animals could be brought on before they developed spontaneously by feeding the dogs upon a rich meat diet, or with salts of ammonia or carbamic acid. Later investigations<sup>2</sup> showed that in normal animals the ammonia contents of the blood in the portal vein are from three to four times what is found in the arterial blood, but that after the operation described the ammonia in the arterial blood increases and at the time of the development of the fatal symptoms

<sup>1</sup> *Archiv für experimentelle Pathologie und Pharmacologie*, 1893, Bd. xxxii. S. 161.

<sup>2</sup> Nencki, Pawlow, and Zaleski: *Ibid.*, 1895, Bd. xxxvii. S. 26; also, Nencki and Pawlow: *Archives des Sciences biologiques*, t. 5, p. 213.

reaches about the percentage which is normal to the blood of the portal vein. It would seem from these investigations that the liver stands between the portal circulation and the general systemic circulation and protects the latter from the comparatively large amount of ammonia compounds contained in the portal blood by converting these compounds to urea. If the liver is thrown out of function, ammonia compounds accumulate in the blood and cause death. The rich amount of ammonia in the portal blood seems to come chiefly from the decomposition of proteid material in the glands of the stomach and pancreas during secretion. Similar ammonia salts are probably formed in other active proteid tissues, since the percentage of ammonia in the tissues is considerably greater than in the blood, and these compounds also are doubtless converted to urea in the liver, in part at least. As to the origin of the ammonia compounds there is little direct evidence. They come in the long run, of course, from the nitrogenous food-stuffs, proteids and albuminoids. Drechsel, having reference to one form only, namely, ammonium carbonate, supposes that the proteids first undergo hydrolytic cleavage, with the formation of amido-bodies, such as leucin, tyrosin, aspartic acid, glycocoll, etc.; that these bodies undergo oxidation in the tissues, with the formation of  $\text{NH}_3$ ,  $\text{CO}_2$ , and  $\text{H}_2\text{O}$ ; and that the  $\text{NH}_3$  and  $\text{CO}_2$  then unite synthetically to form ammonium carbonate, which is carried to the liver and changed to urea. There is reason to believe that the formation of ammonia compounds takes place in the tissues generally.

2. Even after the removal of the liver some urea is still found in the urine. This fact proves that other organs are capable of producing urea, but what the other organs are and by what process they make urea are points yet undetermined. It seems probable that some of the ammonia compounds which are now known to be formed in the tissues generally and to be given off to the blood may be converted into urea elsewhere than in the liver. Just as the glycogenic function of the liver-cells is shared to a less extent by other tissues—e. g. the muscle-fibres—it is possible that their power of converting ammonia salts to urea may be possessed to a lesser degree by other cells, and for this reason removal of the liver is not followed at once by a fatal result. Concerning this point, however, we must wait for further investigation. Drechsel has recently called attention to a method of obtaining urea directly from proteid outside of the body. His method is interesting not only because it is the first laboratory method discovered of producing urea from proteid, but also because it is possible that substantially the same process may occur inside the body. The method consists, in brief, in first boiling the proteid with an acid;  $\text{HCl}$  was used, together with some metallic zinc, so as to keep up a constant evolution of hydrogen and to exclude atmospheric oxygen. Among the products of decomposition of the proteid thus produced was a substance termed *lysatinin* ( $\text{C}_6\text{H}_{11}\text{N}_3\text{O}$ ), and when this body was isolated and treated with boiling baryta-water ( $\text{Ba}(\text{OH})_2$ ) some urea was obtained. It is to be noted that in this case the urea was obtained not by the oxidation of the proteid, but by a series of decompositions or cleavages of the proteid molecule.



Now, lysatinin occurs also in the body as one of the products of the continued action of trypsin on proteids (see p. 303). It is possible, therefore, that by further hydrolysis this substance, when it occurs, is converted to urea, and that normally a part of the urea arises from proteids by this process.

**Uric Acid and Xanthin Bodies.**—Uric acid, which has the formula  $C_5H_4N_4O_3$ , is found constantly, but in relatively small quantities, in human urine and in the urine of mammals generally. The total quantity in the urine of man under normal conditions varies from 0.2 to 1 gram every twenty-four hours. In the urine of birds and reptiles it forms the chief nitrogenous constituent. In these animals it takes the place physiologically of urea in mammalia in that it represents the main end-product of the metabolism of the proteids in the body. It is evident that at some point in the process the metabolism of the proteids in mammalia differs from that in birds and reptiles, since in the one urea, and in the other uric acid, is the outcome. Uric acid occurs in such small quantities in mammals that its place of origin has been investigated with difficulty. Among birds and reptiles uric acid represents the chief nitrogenous excretion of the urine, taking the place physiologically of urea in the mammalia. As in the case of urea, it has been shown that in birds uric acid originates in the liver. Extirpation of the kidneys in these animals leads to an accumulation of uric acid in the blood and tissues. Removal of the liver, on the contrary, causes a decrease in the excretion of uric acid and an increase in the ammonia contents of the urine. It may be concluded, therefore, that in birds uric acid is formed in part in the liver from ammonia compounds (ammonium lactate). Reasoning from analogy, we should suppose that in the mammalia uric acid has a similar origin, but experiments fail to support this view. When a mammal is fed with ammonium lactate or urea there is no increase in the excretion of uric acid. Within recent years a new hypothesis has been advanced by Horbacewsky,<sup>1</sup> and considerable experimental evidence has since given material support to his views.<sup>1</sup> According to Horbacewsky, uric acid may be regarded as a specific end-product of the nucleins contained in the nuclei of cells, and is formed by an oxidation of a grouping in the nuclein which may also give rise to other members of the class of so-called alloxuric bases, such as xanthin, hypoxanthin, or adenin. Feeding a man with food rich in nucleins—the thymus gland, for instance—leads to a marked increase in the excretion of uric acid, and feeding with one, at least, of the alloxuric bases, hypoxanthin, gives a similar result. On this view uric acid should give an indication of the extent of the katabolism or disintegration of the cell-nuclei, especially perhaps in the lymphoid tissue. It is probable, however, that the actual amount of uric acid excreted in the urine does not represent truly the entire amount formed in the body. When uric acid is fed to an animal it does not all reappear in the urine, indicating that this substance may undergo metabolism in the body to a limited extent, its nitrogen appearing probably as urea. Possibly, therefore, some of the uric acid normally produced in the body undergoes a similar fate, only a portion escaping in the urine.

<sup>1</sup> Minkowski: *Archiv für experimentelle Pathologie und Pharmacologie*, Bd. 41, S. 375.

Xanthin ( $C_5H_4N_4O_2$ ), hypoxanthin ( $C_5H_4N_4O$ ), guanin ( $C_5H_4N_4ONH$ ), and adenin ( $C_5H_4N_4NH$ ) are substances closely related to uric acid, and are found in traces in the urine. Since they also originate in the disintegration of nucleins, it is probable that their physiological significance is the same as that of uric acid, and that to the extent to which they occur they also represent an end-product of the katabolism of cell-nuclei. These bodies are found in greatest quantity in muscle, and are present, therefore, in meat-extracts. It is interesting in this connection to call attention to the fact that theobromin (dimethyl-xanthin) and caffen (trimethyl-xanthin) are closely related to the xanthin bodies.

**Creatinin.**—Creatinin ( $C_4H_7N_3O$ ) is a crystalline nitrogenous substance constantly found in urine. It is closely related to creatin ( $C_4H_9N_3O_2$ ), the two substances differing by a molecule of water; the creatin changes to creatinin upon heating with mineral acids. Creatinin occurs in urine to the extent of about 1.12 grams per day in man. In dogs it has been found that the amount may vary between 0.5 and 4.9 grams per day according to the diet, an increase in the amount of meat in the diet causing an increase in the creatinin. This is readily explained by the fact that creatin is a constant constituent of muscle, and when taken into the stomach it is eliminated in the urine as creatinin. It is evident, therefore, that part of the creatinin of the urine is derived from the meat eaten, and does not represent a metabolism within the body. A part, however, comes undoubtedly from the destruction of proteid within the body. In this connection the following facts are suggestive and worthy of consideration, although they cannot be explained satisfactorily: The mass of proteid tissue in the body is found in the muscles, and the end-product of the destructive metabolism of proteid is supposed to be chiefly urea. Nevertheless, urea is not found in the muscles, while creatin occurs in considerable quantities, as much as 90 grams being contained in the body-musculature at any one time. Only a small quantity (1.12 grams) of creatin is eliminated in the urine as creatinin during a day. What becomes of the relatively large quantity of creatin in the muscles? It has been suggested that it is one of the precursors of urea—that it represents an end-product of the proteid destroyed in muscle which is subsequently converted to urea in the liver or elsewhere. This supposition is supported by the fact that creatin may be decomposed readily in the laboratory, with the formation of urea among other products. But against this theory we have the important fact that creatin introduced into the blood is not converted to urea, but is eliminated as creatinin.

**Hippuric Acid.**—This substance has the formula  $C_9H_9NO_3$ . Its molecular structure is known, since upon decomposition it yields benzoic acid and glycocholl, and, moreover, it may be produced synthetically by the union of these two substances. Hippuric acid may be described, therefore, as a benzoyl-amido-acetic acid. It is found in considerable quantities in the urine of herbivorous animals (1.5 to 2.5 per cent.), and in much smaller amounts in the urine of man and of the carnivora. In human urine, on an average diet, about 0.7



gram is excreted in twenty-four hours. If, however, the diet is largely vegetable, this amount may be increased greatly. These last facts are readily explained. It has been found that if benzoic acid or related substances containing this group are fed to animals, they appear in the urine as hippuric acid. Evidently, a synthesis has taken place within the body, and Bunge and Schmiedeberg proved conclusively that in dogs, and probably, therefore, in man, the union of the benzoic acid to glyccoll occurs mainly in the kidney itself. We can understand, therefore, why vegetable foods which are known to contain substances belonging to the aromatic series and yielding benzoic acid should increase the output of hippuric acid in the urine. Since, however, in starving animals or in animals fed entirely on meat hippuric acid is still present, although reduced in amount, it follows that it arises in part as one of the results of body-metabolism. Among the various products of the breaking-down of the proteid molecule, it is probable that some benzoic acid occurs, and, if so, it is excreted in combination with glyccoll as hippuric acid. It should be added, finally, that some of the hippuric acid is supposed to be derived from the process of proteid putrefaction that occurs to a greater or less extent in the large intestine.

**Conjugated Sulphates.**—A good part of the sulphur eliminated in the urine is in the form of ethereal salts with organic compounds of the aromatic and indigo series. Quite a number of these compounds have been described; the most important are the compounds with phenol ( $C_6H_5OSO_2OH$ ), cresol ( $C_7H_7O.SO_2OH$ ), indol ( $C_8H_7NOSO_2OH$ ), and skatol ( $C_9H_7NOSO_2OH$ ). These four substances, phenol, cresol, indol, and skatol, are formed in the intestine during the process of putrefactive decomposition of the proteids (p. 310). They are produced in small quantities, and they may be excreted in part in the feces, but in part they are absorbed into the blood. They are in themselves injurious substances, but it is supposed that in passing through the liver—which must of necessity happen before they get into the general circulation—they are synthetically combined with sulphuric acid, making the so-called “conjugated sulphates,” which are harmless, and which are eventually excreted by the kidneys.

**Water and Inorganic Salts.**—*Water* is lost from the body through three main channels—namely, the lungs, the skin, and the kidney, the last of these being the most important. The quantity of water lost through the lungs probably varies within small limits only. The quantity lost through the sweat varies, of course, with the temperature, with exercise, etc., and it may be said that the amounts of water secreted through kidney and skin stand in something of an inverse proportion to each other; that is, the greater the quantity lost through the skin, the less will be secreted by the kidneys. Through these three organs, but mainly through the kidneys, the blood is being continually depleted of water, and the loss must be made up by the ingestion of new water. When water is swallowed in excess the superfluous amount is rapidly eliminated through the kidneys. The amount of water

secreted may be increased by the action of diuretics, such as potassium nitrate and caffeine.

*The inorganic salts of urine* consist chiefly of the chlorides, phosphates, and sulphates of the alkalis and the alkaline earths. It may be said in general that they arise partly from the salts ingested with the food, which salts are eliminated from the blood by the kidney in the water-secretion, and in part they are formed in the destructive metabolism that takes place in the body, particularly that involving the proteids and related bodies. Sodium chloride occurs in the largest quantities, averaging about 15 grams per day, of which the larger part, doubtless, is derived directly from the salt taken in the food. The phosphates occur in combination with Ca and Mg, but chiefly as the acid phosphates of Na or K. The acid reaction of the urine is usually attributed to these latter substances. The phosphates result in part from the destruction of phosphorus-containing tissues in the body, but chiefly from the phosphates of the food. The sulphates of urine are found partly in an oxidized form as simple sulphates or conjugated with organic compounds, as described above, and in small part in a neutral or unoxidized form, such as potassium sulphocyanide, or ethyl-sulphide,  $(C_2H_5)_2S$ . The total quantity of sulphuric acid eliminated is estimated to average about 2.5 grams per day. Sulphur constitutes a constant element of the proteid molecule, and the quantity of it eliminated in the urine may be used, as in the case of nitrogen, to determine the total destruction of proteid within a given period.

**Functions of the Skin.**—The physiological activities of the skin are varied. It forms, in the first place, a sensory surface covering the body, and interposed, as it were, between the external world and the inner mechanism. Nerve-fibres of pressure, temperature, and pain are distributed over its surface, and by means of these fibres reflexes of various kinds are effected which keep the body adapted to changes in its environment. The physiology of the skin from this standpoint is discussed in the section on Cutaneous Sensations. Again, the skin plays a part of immense value to the body in regulating the body-temperature. This regulation, which is effected by variations in the blood-supply or the sweat-secretion, is described at appropriate places in the sections on Animal Heat, Circulation, and Secretion. In the female, during the period of lactation, the mammary glands, which must be reckoned among the organs of the skin, form an important secretion, the milk; the physiology of this gland is described in the sections on Secretion and Reproduction. In this section we are concerned with the physiology of the skin from a different standpoint—namely, as an excretory organ. The excretions of the skin are formed in the sweat-glands and the sebaceous glands. The sweat-glands are distributed more or less thickly over the entire surface of the body, with the exception of the prepuce and glans penis, while the sebaceous glands, usually in connection with the hairs, are also found everywhere except upon the palms of the hands and the soles of the feet.

**Sweat.**—Sweat, or perspiration, which is the secretion of the sweat-glands, is a colorless liquid with a peculiar odor and a salty taste. Its specific gravity



is given at 1004, and in man it usually has an acid reaction. As can readily be understood, the quantity secreted in twenty-four hours varies greatly, the secretion being influenced by variations in temperature, by exercise, and by psychical and pathological conditions; an average estimate places the daily secretion at from 700 to 900 grams. Chemically, the secretion consists of water and inorganic salts, traces of fats, fatty acid, cholesterin, and urea. Of the inorganic salts, NaCl is by far the most abundant: it occurs in quantities varying from 2 to 3.5 parts per thousand. The elements of the sweat which are of importance from an excretory standpoint are water, inorganic salts, and urea or related nitrogenous compounds. As was said above, sweat constitutes the second in importance of the three main channels through which water is lost from the body. The quantity eliminated in the sweat is to a certain extent inversely proportional to that secreted by the kidneys; but the physiological value of the secretion of water by the sweat-glands seems to lie not so much in the fact that it is necessary in maintaining the water-equilibrium of the blood and tissues as in the important part it takes in controlling the heat-loss from the skin: the greater the evaporation of sweat, the greater the loss of heat. The urea is described as occurring in traces. As far as it occurs, it represents, of course, so much proteid destroyed, but usually in calculating the proteid loss of the body this element has been neglected. Argutinsky demonstrated, however, that in special cases—namely, during periods of unusual muscular work or after vapor-baths—the total weight of nitrogen eliminated by the skin may be of considerable importance, amounting to as much as 0.7 to 0.8 gram. Under ordinary circumstances the excretion of urea and related compounds through the skin must be regarded as of very subsidiary importance, but the amount may be increased markedly under pathological conditions.

**Sebaceous Secretion.**—The sebaceous secretion is an oily, semi-liquid material, the quantity of which cannot be estimated even approximately. Chemically, it consists of water and salts, albumin and epithelium, fats and fatty acids. Its excretory importance in connection with the metabolism of the body must be slight. Its chief physiological value must be sought in its effect upon the hairs, which are kept oiled and pliant by the secretion. Moreover, it forms a thin, oily layer over most of the surface of the skin; and we may suppose that this layer of oil is of value in two ways—in preventing too great a loss of water through the skin, and in offering an obstacle to the absorption of aqueous solutions brought into contact with the skin.

**Excretion of  $\text{CO}_2$ .**—In some of the lower animals—the frog, for example—the skin takes an important part in the respiratory exchanges, eliminating  $\text{CO}_2$  and absorbing O. In man, and presumably in the mammalia generally, it has been ascertained that changes of this kind are very slight. Estimates of the amount of  $\text{CO}_2$  given off from the skin of man during twenty-four hours vary greatly, but the amount is small, and is certainly less than one one-hundredth part of the amount given off through the lungs.

**H. BODY-METABOLISM: NUTRITIVE VALUE OF THE FOOD-STUFFS.**

**Determination of Total Metabolism.**—We have so far studied the changes that the food-stuffs undergo during digestion, the form in which they are absorbed into the blood, their history in the tissues to some extent, and the final condition in which, after being decomposed in the body, they are eliminated in the excreta. To ascertain the true nutritional value of the food-stuffs it is of the utmost importance that we should have some means of estimating accurately the kind and the amount of body-metabolism during a given period in relation to the character of the diet used. Fortunately, this end may be reached by a careful study of the excreta. The methods employed can readily be understood in principle from a brief description. It has been made sufficiently clear before this, perhaps, that by determining the total amount of the nitrogenous excreta we can reckon back to the amount of proteid (or albuminoid) destroyed in the body. In the case of proteids or albuminoids that undergo physiological oxidation all the nitrogen appears in the forms of urea, uric acid, creatinin, xanthin, etc., which are eliminated mainly through the urine, and may therefore be collected and determined. The following practical facts are, however, to be borne in mind in this connection: The nitrogenous excretion of the urine is mainly in the form of urea which can be estimated as such, but it is much more accurate to determine the total nitrogen in the urine during a given period, using some one of the approved methods for nitrogen-determination, and to calculate back from the amount of nitrogen to the amount of proteid. By this means all the nitrogenous excreta which may occur in the urine are allowed for; and since the various proteids differ but little in the amount of nitrogen which they contain, the average being from 15.5 to 16 per cent., it is only necessary to multiply the total quantity of nitrogen found in the excretions by 6.25 (proteid molecule: N :: 100 : 16) to ascertain the amount of proteid destroyed. In accurate calculations it is necessary to determine the total nitrogen in the feces as well as in the urine, and for two reasons: first, in ordinary diets of some vegetable and animal proteid they may escape digestion, and this amount must be determined and deducted from the total proteid eaten in order to ascertain what nitrogenous material has actually been taken into the body; second, the secretions of the alimentary canal contain a certain quantity of nitrogenous material, which represents a genuine excretion, and should be included in estimates of the total proteid-destruction. Recent work seems to show that in ordinary diets most of the nitrogen of the feces has the latter origin. The nitrogen eliminated as urea, etc., in the sweat, milk, and saliva is neglected under ordinary circumstances because the amount is too small to affect materially any calculations made. To determine the total amount of non-nitrogenous material destroyed in the body during a given period, two data are required: first, the total nitrogen in the excreta of the body; second, the total amount of carbon given off from the lungs and in the various excreta. From the total nitrogen one calculates how much proteid was destroyed, and, deducting from the total carbon the amount corresponding to



this quantity of proteid, what remains represents the carbon derived from the metabolism of the non-nitrogenous material—that is, from the fat or carbohydrate. By methods of this kind it is possible to reckon back from the excreta to the total amount of material, consisting of proteid, fat, and carbohydrate, which has been consumed in the body within a certain period. If, now, by analyzing the food or by making use of analyses already made (see p. 278), one determines how great a quantity of proteid, fat, and carbohydrate has been taken into the body in the same period, then, by comparison of the total ingesta and egesta, it is possible to strike a balance and to determine whether all the proteid, fat, and carbohydrate of the food have been destroyed, or whether some of the food has been stored in the body, and in this case whether it is nitrogenous or non-nitrogenous material, or, lastly, whether some of the reserve material of the body, nitrogenous or non-nitrogenous, has been destroyed in addition to the supply of food. It is needless to remark that “balance experiments” of this character are very laborious, particularly as they must be made over long intervals—one or more days. Nevertheless, a great deal of work of this kind has been done upon man as well as upon lower animals, especially by Voit<sup>1</sup> and Pettenkofer. In the experiments upon man the urine and feces were collected carefully and the total nitrogen was determined; at the same time the total quantity of  $\text{CO}_2$  given off from the lungs was estimated for the entire period. The determination of the  $\text{CO}_2$  was made possible by keeping the man in a specially-constructed chamber through which air was drawn by means of a pump; the total quantity of air drawn through was indicated by a gasometer, and a measured portion of this air was drawn off through a separate gasometer and was analyzed for its  $\text{CO}_2$ . It was found that the method is practicable: that by the means described a nearly perfect balance may be struck between the income and the outgo of the body. Experiments of this general character have been used to determine the fate of the food-stuffs in the body under different conditions, the essential part that each food-stuff takes in general nutrition, and so on. In this and the succeeding sections we shall have to consider some of the main results obtained; but first it will be convenient to define two terms frequently used in this connection—namely, “nitrogen equilibrium” and “carbon equilibrium.”

*Nitrogen Equilibrium.*—By “nitrogen equilibrium” we mean that condition of an animal in which, within a definite period, the nitrogen of the excreta is equal in amount to the nitrogen of the food; in other words, that condition in which the proteid (and albuminoid) food eaten exactly covers the loss of proteid (and albuminoid) in the body during the same time. If an animal is giving off more nitrogen in its excreta than it receives in its food, then the animal must be losing proteid from its body; if, on the contrary, the food that it eats contains more nitrogen than is found in the excreta, the animal must be storing proteid in its body. A condition of nitrogen equilibrium is the normal state of a properly-nourished adult. It is important to remember that nitrogen equilibrium may be maintained at different levels; that is, one may

<sup>1</sup> Hermann's *Handbuch der Physiologie*, 1881, Bd. vi.

begin with a starving animal and slowly increase the amount of nitrogenous food until nitrogen equilibrium is just established. If now the amount of nitrogenous food is increased—say doubled—the excess does not, of course, continue to be stored up in the animal's body; on the contrary, in a short time the amount of proteid destroyed in the body will be increased to such an extent that nitrogen equilibrium will again be established at a higher level, the animal in this case eating more and destroying more. The highest limit at which nitrogen equilibrium can be maintained is determined, apparently, by the power of the stomach and the intestines to digest and absorb proteid food. Further details upon this point will be given presently, in describing the nutritive value of the food-stuffs.

*Carbon Equilibrium.*—The term "carbon equilibrium" is sometimes used to describe the condition in which the total carbon of the excreta (occurring in the  $\text{CO}_2$ , urea, etc.) is exactly covered by the carbon of the food. As one can readily understand, an animal might be in a condition of nitrogen equilibrium and yet be losing or be gaining in weight, since, although the consumption of proteids in the body might just be covered by the proteids of the food, the consumption of non-proteids, fats and glycogen, might be greater or less than was covered by the supply of food. In addition, we might speak of an equilibrium as regards the water, salts, etc., although these terms are not generally used. An adult in good health usually so lives as to keep in both nitrogen and general body equilibrium—that is, to maintain his normal weight—while slight variations in weight from time to time are probably for the most part due to a loss or a gain in body-fat—in other words, to changes in the carbon equilibrium.

*Nutritive Importance of the Proteids.*—The digestion and absorption of proteids have been considered in previous sections. We believe that the digested proteid, with the exception of the variable quantity that suffers decomposition in the intestine as a result of putrefaction or of the prolonged action of trypsin, is absorbed into the blood after undergoing an unknown modification during the act of absorption. Subsequently this proteid material passes into the lymph and is brought into contact with the tissues. Its main nutritive importance lies in its relations to the tissues, and, speaking generally, we may say that the final fate of the proteid molecule is that it undergoes a physiological oxidation whereby the complex molecule is broken down to form the simpler and more stable compounds,  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ , urea, sulphates and phosphates. This destruction of the proteid molecule takes place in or under the influence of the living cells, and it gives rise to a liberation of energy mainly in the form of heat. It is impossible to follow the various ways in which this physiological oxidation takes place. It is probable, however, that some of the proteid undergoes destruction without becoming a part, an organized part, of the living cells, although its oxidation is effected through the agency of the cells. It has been proposed by Voit<sup>1</sup> to designate the proteid that is oxidized in this way as

<sup>1</sup> *Herrmann's Handbuch der Physiologie*, 1881, Bd. vi. S. 300.



"the circulating albumin or proteid." According to Voit, a well-fed animal has in its lymph and tissues always a certain excess of proteid which is to undergo the fate of the circulating proteid, and this supposition is used to explain the fact that for the first day or so a starving animal metabolizes more proteid, as determined by the nitrogenous excreta, than in the subsequent days, after the supply of the circulating proteid has been destroyed. A portion of the proteid food, however, before its final destruction is utilized to replace the nitrogenous waste of the tissues; it is built up into living protoplasm to supply the place of organized tissue that has undergone disassimilation or to furnish new tissue in growing animals. To the proteid that is built up into tissue Voit gives the name of "*organeiwiss*," the best translation of which, perhaps, is "tissue-proteid." It should be stated that this division of the proteid into circulating proteid and tissue-proteid has been severely criticised by some physiologists, but it has the merit at least of furnishing a simple explanation of some curious facts with regard to the use of proteid in the body. To avoid misunderstanding, it is well to say that the separation into circulating proteids and tissue-proteids does not mean that the proteid that is absorbed from the alimentary canal is of two varieties. The terms refer to the final fate of the proteid in the body: a certain portion is utilized to replace protoplasmic tissue, and it then becomes "tissue-proteid," while the balance is metabolized in various ways and constitutes the "circulating proteid." Any given molecule of proteid, as far as is known, may fulfil either function. With regard to the general nutritive value of proteids, it has been demonstrated clearly that they are absolutely necessary for the formation of protoplasmic tissue. An animal fed only on non-nitrogenous food such as fats and carbohydrates will inevitably starve to death in time: this has been shown by actual experiments, and, besides, it follows from *a priori* considerations. Protoplasm contains nitrogen; fats and carbohydrates are non-nitrogenous, and therefore cannot be used to make new protoplasmic material. It is requisite, moreover, not only that the food shall contain some nitrogen, but that this nitrogen shall be in the form of proteid. If an animal is fed upon a diet containing fats and carbohydrates and nitrogenous material other than proteids, such as amido-acids or gelatin, nitrogenous equilibrium cannot be maintained. There will be a steady loss of nitrogen in the excreta, due to a breaking-down of proteid tissue within the body, and the final result of maintaining such a diet would be the death of the animal. It may be said, then, with regard to animal metabolism that proteid food is absolutely necessary for the formation of new protoplasm: its place in this respect cannot be taken by any other element of our food. But, in addition to this use, proteid, as has been described above, may be oxidized in the body without being first constructed into protoplasmic material. According to an older theory in physiology, advanced by Liebig, food-stuffs were either plastic or respiratory; by plastic foods he meant those that are built into tissue, and he supposed that the proteids belonged to this class; by respiratory foods he meant those that are oxidized or burnt in the body to produce heat: the fats and

carbohydrates constituted this class. We now know that proteids are respiratory as well as plastic in the terms of this theory; they serve as sources of energy as well as to replace tissue, and Liebig's classification has therefore fallen into disuse. Our present ideas of the twofold use of proteid food may be supported by many observations and experiments, but perhaps the most striking proof of the correctness of these views is found in the fact that a carnivorous animal can be kept in both nitrogen and carbon equilibrium upon a meat diet only, excluding for the time a consideration of the water and inorganic salts. Pettenkofer and Voit kept a dog weighing 30 kilograms in nitrogen and carbon equilibrium upon a diet of 1500 grams of lean meat per day, and by increasing the diet to 2500 grams per day the animal even gained in weight, owing to an increase in fat. Pflüger states also that he was able to keep a dog in body-equilibrium as long as eight months upon a meat diet. Facts like these demonstrate that the animal organism may get all its necessary energy from proteid food alone, although, as we shall see later, it is more economical and more beneficial to get a part of it at least from the oxidation of fats and carbohydrates. Adopting the theory of "circulating proteids," we may say that any excess of proteid above that utilized for tissue-repair or tissue-growth will be metabolized in the body, with the liberation of energy. It makes no difference how much proteid material we consume: the excess beyond that used to replace tissue is quickly destroyed in some way, and its nitrogen appears in the urine as urea or one of the related compounds. A good example of the power of the tissues to oxidize large amounts of proteid is given in the following experiment, selected from a paper by Pflüger. Dog, weight 28.1 kilograms, fed at 11 A. M. with 2070.7 grams of meat:

2070.7 grams of meat contain . . . . .	69.2 grams N.
Total nitrogen eliminated in urine and feces in twenty-four	
hours (7 A. M. to 7 A. M.) . . . . .	71.2 " "
Deficit of N . . . . .	0.96 grams.

The total nitrogen in the urine alone was 68.5 grams.

In urine from 7 A. M. to 11 A. M., the fasting period . . . . .	6.9 grams.
In urine from 11 A. M. to 7 A. M., time after feeding . . . . .	61.6 "

Therefore in the four hours of fasting the animal eliminated in his urine 1.7 grams N per hour, while in the twenty hours after eating he excreted 3.1 grams N per hour. This experiment shows not only the completeness with which an excessive proteid diet is handled by the tissues, but also the rapidity with which the excess is destroyed. In so far as proteid food is burnt in the body only as a source of energy and without being used to form new tissue, its place can be supplied in part, but only in part, by non-nitrogenous food-stuffs—carbohydrates and fats. The double use of proteid as a tissue-former and an energy-producer would seem to imply that if, in any given case, sufficient proteid were used in the diet to cover the tissue-waste, the balance of the diet might be composed of fats and carbohydrates, and the animal thereby be kept in nitrog-



enous equilibrium. Apparently this is not the case, as is seen from experiments of the following character: When an animal is allowed to starve, the nitrogen in the urine, after the first few days, becomes practically constant, and represents the amount of oxidation of proteid tissue taking place in the body. If, now, the animal is given an amount of proteid just equal to that being destroyed in the body, nitrogenous equilibrium is not established; some of the body-proteid continues to be lost, and to get the animal into equilibrium a comparatively large excess of proteid must be given in the food. The same result holds if carbohydrates and fats are given along with the proteid, with the exception that upon this diet nitrogen equilibrium is more readily established—that is, less proteid is required in the food. Upon the theory of circulating proteids and tissue-proteids, this fact may be accounted for by saying that of the proteid given as food, a part always undergoes destruction as circulating proteid without going to form tissue, so that to cover tissue-waste a larger amount of proteid must be taken as food than would be necessary if it could all be used exclusively for the repair of tissue. Carbohydrates and fats diminish the amount of proteid destroyed as circulating proteid, and thereby enable us to keep in nitrogen equilibrium on a smaller proteid diet. With albuminoid food (gelatin) the facts seem to be different. If albuminoids be given in the food together with proteids or with proteids and a non-nitrogenous food-stuff (fats or carbohydrates), nitrogen equilibrium may be established upon a much smaller amount of proteid than in the case of a diet consisting of proteid alone or of proteid together with fats and carbohydrates. It seems probable that albuminoids can take the place entirely of circulating proteids, so that only enough proteid need be given to cover actual tissue-waste. This point will be referred to again in speaking of the value of the albuminoids.

*Luxus Consumption.*—The fact that normally more proteid is eaten, even in a mixed diet, than is necessary to cover the actual tissue-waste led some of the older physiologists to speak of the excess as unnecessary, a *luxus*, and the rapid destruction of the excess in the body was described as a “*luxus consumption*.” There can be no doubt about the fact that proteid may be, and normally is, eaten in excess of what is necessary to repair tissue-waste, or in excess of what is requisite to maintain nitrogenous equilibrium at a low level. But it is altogether improbable that the excess is really a “*luxus*.” It has been stated, in speaking of nitrogenous equilibrium, that an animal may be kept in this condition upon a certain minimal amount of proteid, or upon various larger amounts up to the limit of the power of the alimentary canal to digest and absorb; but it has also been shown (Munk<sup>1</sup>) that if an animal is fed upon a diet containing quantities of proteid barely sufficient to maintain N equilibrium, it will after a time show signs of malnutrition. It seems to be necessary, as Pflüger pointed out, that the tissues should have a certain excess of proteid to destroy in order that their nutritional or metabolic powers may be kept in a condition of normal activity. Hence we find that well-nourished individuals habitually consume more proteid than would theoretically suffice for N equilibrium. For example, the average

<sup>1</sup> Du Bois-Reymond's *Archiv für Physiologie*, 1891, 8, 338.

diet of an adult male contains, or should contain, from 100 to 118 grams of proteid per day, but it has been shown that nitrogen and body equilibrium in man may be maintained, for short periods at least, upon 40 or even 20<sup>1</sup> grams of proteid a day, provided large amounts of fats or carbohydrates are eaten. It is scarcely necessary to add that this beneficial excess has a limit, and that too great an excess of proteid food may cause troubles of digestion as well as of general nutrition.

**Nutritive Value of Albuminoids.**—The albuminoid most frequently occurring in food is gelatin. It is derived from *collagen* of the connective tissues. Collagen of bones or of connective tissue takes up water when boiled and becomes converted into gelatin. We eat gelatin, therefore, in boiled meats, soups, etc., and, besides, it is frequently employed directly as a food in the form of table-gelatin. Collagen has the following percentage composition: C, 50.75 per cent.; H, 6.47; N, 17.86; O, 24.32; S, 0.6. It resembles the proteid molecule closely in percentage composition, and it would seem that the tissues might use it as they do proteid, for the formation of new protoplasm. Experiments, however, have demonstrated clearly that this is not the case. Animals fed upon albuminoids together with fats and carbohydrates do not maintain N equilibrium; a certain proportion of tissue breaks down, giving an excess of nitrogen in the urine. The final result of such a diet would be continued loss of weight and, finally, malnutrition and death. Gelatin, however, is readily digested, gelatoses and gelatin peptones being formed; these are absorbed and oxidized in the body, with the formation of CO<sub>2</sub>, H<sub>2</sub>O, and urea or some related nitrogenous product. Gelatin serves, then, as a source of energy to the body in the same sense as do carbohydrates and fats. When any one of these three substances is used in a diet, the proportion of proteid necessary for the maintenance of N equilibrium may be reduced greatly. Upon the theory of circulating proteids, this is explained by saying that these substances are burnt in place of proteid, and that the proportion of this latter material which undergoes the fate of circulating proteid is thereby diminished. Actual experiments have shown that gelatin is more efficacious than either fats or carbohydrates in protecting the proteid in the body, and it has been suggested, therefore, that it may take the place, partly or completely, of the circulating proteid, according to the amount fed. If this suggestion is true, we may say that gelatin has a nutritive value the same as that of the proteids, except that it cannot be constructed into living proteid. The relative value of fats, carbohydrates, and gelatin in protecting proteid from destruction in the body is illustrated by the following experiment, reported by Voit. A dog weighing 32 kilograms was fed alternately upon proteid and sugar, proteid and fat, and proteid and gelatin:

Meat.	Nourishment (grams).			Calculated destruction of flesh in body (grams).
	Gelatin	Fat.	Sugar.	
400	—	200	—	450
400	—	—	250	439
400	200	—	—	356

<sup>1</sup> Siven: *Skandinavisches Archiv für Physiologie*, 1899, Bd. 10, S. 91.



Practically, however, the use of gelatin in diets is restricted by its unpalatableness when used in large quantities. Whatever may be the physiological cause of this peculiarity, there seems to be no doubt that when employed largely in the diet both animals and men soon develop such an aversion to it that it is necessary to discontinue its use. Munk<sup>1</sup> has attempted to determine how far the proteids of food may be replaced by gelatin. In these experiments a dog was brought into a condition of nitrogenous equilibrium upon a diet of flesh, meal, rice, and lard, containing 9.73 grams of nitrogen. During the period this diet was continued the animal, whose weight was 16.5 kilograms, was oxidizing in its body 3.7 grams of proteid daily for each kilogram of weight. In a second period lasting four days the quantities of rice and lard were the same as before, but the proteid in its diet was reduced to 8.2 grams, which contained 1.3 grams of nitrogen; the balance of the necessary nitrogen was supplied in the form of gelatin, so that in round numbers only one-seventh of the required daily amount of nitrogen was given as proteid. The result was that the animal maintained its nitrogen equilibrium for the short period stated. It was found that the experiments could not be continued longer than four days, owing to the growing dislike of the animal for the gelatin food. During the second period the animal was receiving in its food and burning in its body only 0.5 gram of proteid daily for each kilogram of weight, as against 3.7 grams upon a normal diet. It is usually stated that it is not possible to substitute fats or carbohydrates for the proteids of our diet to the same extent, but the experiments of Sivén quoted on the preceding page indicate that this common belief may be incorrect.

**Nutritive Value of Fats.**—The fats of food are absorbed into the lacteals as neutral fats. They eventually reach the blood in this condition, and are afterward in some way consumed by the tissues. The final products of their oxidation must be the same as when burnt outside the body—namely,  $\text{CO}_2$  and  $\text{H}_2\text{O}$ —and a corresponding amount of energy must be liberated. Speaking generally, then, the essential nutritive value of the fats is that they furnish energy to the body, and, from a chemical standpoint, they must contain more available energy, weight for weight, than the proteids or the carbohydrates (see p. 365). In a well-nourished animal a large amount of fat is found normally in the adipose tissues, particularly in the so-called “*panniculus adiposus*” beneath the skin. Physiologically, this body-fat is to be regarded as a reserve supply of nourishment. When food is eaten and absorbed in excess of the actual metabolic processes of the body, the excess is stored in the adipose tissue as fat, to be drawn upon in case of need—as, for instance, during partial or complete starvation. A starving animal, after its small supply of glycogen is exhausted, lives entirely upon body-proteids and fats; the larger the supply of fat, the more effectively will the proteid tissues be protected from destruction. In accordance with this fact, it has been shown that when subjected to complete starvation a fat animal will survive longer than a lean one. Our supply of fat is called upon not only during complete abstinence from food, but also whenever the diet is insufficient to cover the oxidations of the body, as in deficient food, sickness, etc.

<sup>1</sup> *Pflüger's Archiv für die gesammte Physiologie*, 1894, Bde. lvi.ii S. 309.

**Formation of Fat in the Body.**—The origin of body-fat has always been an interesting problem to physiologists. Naturally, the first supposition made was that it comes directly from the fat of the food. According to this view, a certain proportion of the fat of the food was supposed to be deposited directly in the cells of adipose tissue, and in this way all our supply of fat originated. This theory was soon disproved. It was shown, especially upon cows and pigs, that the amount of fat formed in the body within a given time, including the fat of milk in the case of the cow, might be far in excess of the total amount of fat taken in the food during the same period, thus demonstrating that a certain proportion at least of the body-fat must have some other origin. Moreover, the genesis of the fat-droplets in fat-cells, as studied under the microscope, did not agree with the old view; and there was the further fact that each animal has its own peculiar kind of fat; as Liebig says, "In hay or the other fodder of oxen no beef-suet exists, and no hog's lard can be found in the potato refuse given to swine." In fact, the evidence was so conclusive against this theory that physiologists for a time were led to adopt the opposite view that no fat at all can be obtained directly from the fat of the food. However, it has now been shown that under certain conditions fat may be deposited directly in the tissues from the fat of food. Lebedeff, and afterward Munk, proved that if a dog is first starved until the reserve supply of fat in the body is practically used up, and it is then fed richly upon foreign fats, such as rape-seed oil, linseed oil, or mutton tallow, it will again lay on fat, and some of the foreign fat may be detected in its body. The conditions necessary to be fulfilled in order to get this result make it probable that under normal conditions none of the fat of the body is derived directly from the fat of the food. On the contrary, the fat of the food is completely oxidized, and our body-fat is normally constructed anew from either proteids or carbohydrates. As to its origin from proteid, Voit has devoted numerous researches to the purpose of demonstrating that this is the main source of body-fat. His belief is that in the course of metabolism the proteid molecule undergoes a cleavage, with the formation of a nitrogenous and a non-nitrogenous part. The former, after further changes, is eliminated in the form of urea, etc.; the latter may be converted into fat, or possibly into glycogen. The theoretical maximum of fat which can arise in this way is 51.5 per cent. of the entire amount of proteid. Voit attempted to demonstrate this theory by actual experiments. He showed that dogs fed upon large amounts of lean meat did not give off as much carbon in the excreta as they received in the food. The excess of carbon must have been retained in the body, and, in all probability, in the form of fat. As corroborative evidence he cites the apparently direct conversion of proteid material into fat in such cases as the formation of fat-droplets in the fat-cells or cells of the mammary glands, and in muscle-fibres and liver-cells undergoing fatty degeneration; but evidence of this latter character is not conclusive, since we have no immediate proof that the fat arises directly from the proteid material in the cells. Voit's experimental evidence has been questioned recently by Pflüger, his criticisms being directed mainly toward the calculations involved



in Voit's experiments. The result of this criticism has been to make us more cautious in attributing the origin of body-fat solely or mainly to proteids, but as regards the possibility of some proteid being converted into fat in the body there can be no reasonable doubt. It has been proved (p. 328) that glycogen may be formed from proteid, and since it is now generally accepted that fats are formed from carbohydrates, the possibility of an indirect production of fats from proteids seems to follow necessarily.

The connection between the carbohydrates of the food and the fat of the body has been a subject of discussion and investigation among physiologists for a number of years. It was the original belief of Liebig that carbohydrates are the source of body-fat. This view was afterward abandoned under the influence of the work of Pettenkofer and Voit, but renewed investigations seem to have re-established it upon solid experimental grounds. In some older experiments of Lawes and Gilbert it was shown that the fat laid on by a young pig during a certain period was greater than could be accounted for by the total fat in the food during that period, plus the theoretical maximum obtainable from the proteid fed during the same time. Of more recent experiments demonstrating the same point, a single example may be quoted from Rubner,<sup>1</sup> as follows: A small dog, weighing 6.2 kilograms, was fed richly with meat for two days and was then starved for two days; its weight at the end of this time was 5.89 kilograms. The animal was then given for two days a diet of cane-sugar 100 grams, starch 85 grams, and fat 4.7 grams. It was kept in a respiration apparatus and its total excretion of nitrogen and carbon was determined:

Total C excretion . . . . .	87.10	grams C.
" C ingesta . . . . .	176.6	" "
	<u>89.5</u>	" " retained in the body

The total nitrogen excreted = 2.55 grams. The carbon contained in the proteid thus broken down plus that in the 4.7 grams of fat = 13 grams. If we make the assumption that all of the C from these two sources was retained within the body, there would still be a balance of 76.5 grams C (89.5 — 13.0) which must have been stored in the body either as glycogen or as fat. The greatest possible storage of glycogen was estimated at 78 grams = 34.6 grams C, so that 76.5 — 34.6 = 41.9 grams C as the minimal amount which must have been retained as fat and must have arisen from the carbohydrates of the food. Similar experiments have been made upon herbivorous animals, and as the result of investigations of this character we are compelled to admit that the carbohydrates form one source, and possibly the main source, from which the body-fats are derived. This belief accords with the well-known fact that in fattening stock the best diet is one containing a large amount of carbohydrate together with a certain quantity of proteid. On the view that fats were formed only from proteids, the efficacy of the carbohydrates in such a diet was supposed to lie in the fact that they protected a part of the proteid from oxidation, and thus permitted the formation of fat from proteid; but it is now believed that the carbohydrates of a fattening diet are, in part, converted

<sup>1</sup> *Zeitschrift für Biologie*, 1886, Bd. 22, S. 272.

directly to fat, although the chemistry of the transformation is not as yet understood. Diets, such as the well-known Banting diet, intended to reduce obesity are characterized, on the contrary, by a small proportion of carbohydrates and a relative excess of proteid.

**Nutritive Value of Carbohydrates.**—The nutritive importance of the carbohydrates is similar in general to that of the fats; they are oxidized and furnish energy to the body. In addition, as has been described in the preceding paragraph, they may be converted into fat and stored in the body as a reserve supply of nourishment. As a matter of fact, the carbohydrates form the bulk of ordinary diets. They are easily digested, easily oxidized in the body, and from a financial standpoint they form the cheapest food-stuff. The final products in the physiological oxidation of carbohydrates must be  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . Inasmuch as the H and O in the molecule already exist in the proper proportions to form  $\text{H}_2\text{O}$  ( $\text{C}_6\text{H}_{12}\text{O}_6$ ,  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$ ), it follows that relatively less oxygen will be needed in the combustion of carbohydrates than in the case of proteids or of fats. Whatever may be the actual process of oxidation, we may consider that only as much O is needed as will suffice to oxidize the C of the sugar to  $\text{CO}_2$ .

Hence the ratio of O absorbed to  $\text{CO}_2$  eliminated,  $\frac{\text{CO}_2}{\text{O}_2}$ , a ratio that is known as the respiratory quotient, will approach nearer to unity as the quantity of carbohydrates in the diet is increased. From our study of the digestion of carbohydrates (p. 318) we have found that most of the carbohydrates of our food pass into the blood as dextrose (or levulose), and any excess above a certain percentage is converted temporarily to glycogen in the liver, the muscles, etc., to be again changed to dextrose before being used. The sugar undergoes final oxidation in the tissues to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . While it is possible that this oxidation may be direct—that is, that the sugar may be burnt directly to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ —it is usually supposed to be preceded by a splitting of the sugar molecule, although the steps in the process are not definitely known.

There has been discovered recently in connection with the pancreas a number of facts that are interesting not only in themselves, but doubly so because they promise, when more fully investigated, to throw some light on the manner of consumption of sugar by the tissues. (See also section on Internal Secretions.) It has been shown by von Mering and Minkowski<sup>1</sup> and others that if the pancreas of a dog is completely removed, the tissues lose the power of consuming sugar, so that it accumulates in the blood and finally escapes in the urine, causing what has been called "pancreatic diabetes." If a small part of the pancreas is left in the body, even though it is not connected by its duct with the duodenum, diabetes does not occur. The inference usually made from these experiments is that the pancreas gives off something to the blood—an internal secretion—that is necessary to the physiological consumption of sugar. In what way the pancreas exerts this influence has yet to be discovered; possibly it is through the action of a specific enzyme that helps to break down the sugar; possibly it is by some other means. But the necessity of

<sup>1</sup> *Archiv für experimentelle Pathologie und Pharmacologie*, 1893, **xxi**, 8, 85.



the pancreas in some way for the normal consumption of sugar by the tissues generally seems to be indisputably established. It is a discovery of the utmost importance in its relations to the normal nutrition of the body, and also because of its possible bearing on the pathological condition known as *diabetes mellitus*. In this latter disease the tissues, for some reason, are unable to oxidize the sugar in normal amounts, and a good part of it, therefore, escapes through the urine. The facts and theories bearing upon diabetes are of unusual interest in connection with the nutritive history of the carbohydrates, but for a fuller description reference must be made to more elaborate works.

Another statement in connection with the fate of sugar in the body is worthy of a brief reference: It has been asserted by Lepine and Barral that there is normally present in blood an enzyme capable of destroying sugar. Their theory rests upon the undoubted fact that sugar added to blood outside the body soon disappears. They call the process "glycolysis," and the enzyme to which they attribute this disappearance the "glycolytic enzyme." Others, however (Arthus), have claimed that this enzyme is only a post-mortem result of the disintegration of the corpuscles of the blood, and that it is not present in circulating blood. We must await further investigation upon this point, and be content here with a mere reference to the subject.

**Nutritive Value of Water and Salts.**—Water is lost daily from the body in large quantities through the kidney, the skin, the lungs, and the feces, and it is replaced by water taken in the food or separately, and partially also by the water formed in the oxidations of the body. A certain percentage of water in the tissues and in the liquids of the body is naturally absolutely essential to the normal play of metabolism; and conditions, such as muscular exercise, that increase the water-loss bring about also an increased water-consumption, the regulation being effected through the nervous mechanism that mediates the sensation of thirst. The water taken into the body does not, however, serve directly as a source of energy, since it is finally eliminated in the form in which it is taken in; it serves only to replace water lost from the tissues and liquids of the body, and it furnishes also the menstruum for the varied chemical reactions that take place. Continued deprivation of water leads to intolerable thirst, the cause of which is usually referred to the altered composition of the tissues generally, including the peripheral nervous system.

**Inorganic Salts.**—The essential value of the inorganic salts to the proper nutrition of the body does not commonly force itself upon our attention, since, as a rule, we get our proper supply unconsciously with our food, without the necessity of making a deliberate selection. NaCl (common table-salt) forms an exception, however, to this rule. Speaking generally, inorganic salts do not serve as a source of heat-energy to the body—that is, the reactions that they may undergo are not accompanied by the transformation of a material amount of chemical energy into heat. On the other hand, their presence and distribution by virtue of their osmotic pressure may exercise an important influence upon the movement of water in the body. Most of the salts found in the urine and other excreta are eliminated in the same form in which they

were received into the body. Some of them, however, notably the phosphates and the sulphates, are formed in the course of the metabolism of the tissues, and without doubt reactions of various kinds occur affecting the composition of many of the salts—for example, the decomposition of the chlorides to form the HCl of gastric juice. But these reactions do not materially influence the supply of energy in the body: the value of the salts lies in the general fact that they are necessary to the maintenance of the normal physical and chemical properties of the tissues and the body-fluids. Experimental investigation<sup>1</sup> has shown in a surprising way how immediately important the salts are in this respect. Forster fed dogs and pigeons on a diet in which the saline constituents had been much reduced, although not completely removed. The animals were given proteids, fats, and carbohydrates, but they soon passed into a moribund condition. It seemed, in fact, that the animals died more quickly on a diet poor in salts than if they had been entirely deprived of food. Similar experiments were made by Lunin upon mice, with corresponding results. He showed, moreover, that while mice live very well upon cow's milk alone, yet if given a diet almost free from inorganic salts, consisting of the casein and fats of milk plus cane-sugar, they soon died. Moreover, if all the inorganic salts of milk were added to this diet in the proportion in which they exist in the ash of milk, the mixture still failed to support life. It would seem from this result that the inorganic salts cannot fulfil completely their proper functions in the body unless they exist in some special combination with the organic constituents of the food. In this connection it is well to bear in mind that proteids as they occur in nature seem always to be combined with inorganic salts, and the properties of proteids, as we know them, are undoubtedly dependent in part upon the presence of this inorganic constituent. We may assume that the original synthesis of the organic and inorganic constituents is made in the plant kingdom, and that, in its own way, the inorganic constituent of the molecule is as necessary to the proper nutrition of the animal tissues as is the organic. One salt (NaCl) is consumed by many animals, including man, in excess of the amount unconsciously ingested with the food. Bunge points out that purely carnivorous animals are not known to crave this salt, while the herbivora with some exceptions—for example, the rabbit—take it at times largely in excess. The need of salt on the part of these animals is well illustrated among the wild forms by the eagerness with which they visit salt-licks. Bunge advances an ingenious theory to account for the difference between the herbivora and the carnivora in regard to the use of salt. He points out that in plant food there is a relatively large excess of potassium salts. When these salts enter the liquids of the body they react with the NaCl present and a mutual decomposition ensues, with the formation of KCl and the sodium salt of the acid formerly combined with the potassium, and the new salts thus formed are eliminated by the kidneys as soon as they accumulate beyond the normal limit.

<sup>1</sup> Bunge: *Physiological and Pathological Chemistry*, translated by Wooldridge, 1890.



In this way the normal proportion of NaCl in the tissues and the body-fluids is lowered and a craving for the salt is produced. Bunge states that it has been shown among men that vegetarians habitually consume more salt than those who are accustomed to eat meats. The salts of calcium and of iron have also a special importance that needs a word of reference. The particular importance of the iron salts lies in their relation to hæmoglobin. The continual formation of new red blood-corpuscles in the body requires a supply of iron salts for the synthesis of the hæmoglobin, and, although there is a probability (see p. 323) that the iron compound of the disintegrating corpuscles is again used in part for this purpose, we must suppose that the body requires additional iron in the food from time to time to take the place of that which is undoubtedly lost in the excretions. It has been shown that iron is contained in animal and vegetable foods in the form of an organic compound, and the evidence at hand goes to show that only when it is so combined can the iron be absorbed readily and utilized in the body, while the efficacy of the inorganic salts of iron as furnishing directly a material for the production of hæmoglobin is, to say the least, open to doubt. Bunge isolated from the yolk of eggs an iron-containing nuclein which he calls *hæmatogen*, because in the developing hen's egg it is the only source from which the iron required for the production of hæmoglobin can be obtained. It is possible that similar compounds occur in other articles of food. Most of the iron taken with food, however, including that present in the hæmoglobin of meats, passes out in the feces unabsorbed. It is probable that there is an actual excretion of iron from the body, and, so far as known, this excretion is effected in small part through the urine and bile, but mainly through the walls of the intestine, the iron being eliminated finally in the feces. The large proportion of calcium salts found in the skeleton implies a special need of these salts in the food, particularly in that of the young. It has been shown that if young dogs are fed upon a diet poor in Ca salts, the bones fail to develop properly, and a condition similar to rickets in children becomes apparent. In addition to their relations to bone-formation and the fact that they form a normal constituent of the tissues and liquids of the body, calcium salts are necessary to the coagulation of blood (see p. 57), and, moreover, they seem to be connected in some intimate way with the rhythmic contractility of heart-muscle, and, indeed, with the normal activity of protoplasm in general, animal as well as plant. Notwithstanding the special importance of calcium in the body, no great amount of it seems to be normally absorbed or excreted. Voit has shown that the calcium eliminated from the body is excreted mainly through the intestinal walls, but that most of the Ca in the feces is the unabsorbed Ca of the food. It is possible that the Ca must be present in some special combination in order to be absorbed and utilized in the body. A point of special interest in connection with the nutritive value of the inorganic salts was brought out by Bunge in some analyses of the body-ash of sucking animals in comparison with analyses of the milk and the blood of the mother. In the

case of the dog he obtained the following results (mineral constituents in 100 parts of ash):

	Young Pup.	Dog's Milk.	Dog's Serum.
K <sub>2</sub> O . . . . .	8.5	10.7	2.4
Na <sub>2</sub> O . . . . .	8.2	0.1	52.1
CaO . . . . .	35.8	34.4	2.1
MgO . . . . .	1.6	1.5	0.5
F <sub>2</sub> O <sub>3</sub> . . . . .	0.34	0.14	0.12
P <sub>2</sub> O <sub>5</sub> . . . . .	39.8	37.5	5.9
Cl . . . . .	7.3	12.4	47.6

The remarkable quantitative resemblance between the ash of milk and the ash of the body of the young indicates that the inorganic constituents of milk are especially adapted to the needs of the young; while the equally striking difference between the ash of milk and the ash of the maternal blood seems to show that the inorganic salts of milk are formed from the blood-serum not simply by diffusion, but rather by some selective secretory act. These facts come out most markedly in connection with the CaO and the P<sub>2</sub>O<sub>5</sub>. For further details as to the history of calcium and iron in the body, consult the section on Chemistry of the Body, under *calcium* and *iron*.

#### I. ACCESSORY ARTICLES OF DIET; VARIATIONS OF BODY-METABOLISM UNDER DIFFERENT CONDITIONS; POTENTIAL ENERGY OF FOOD; DIETETICS.

**Accessory Articles of Diet.**—By accessory articles of diet we mean those substances that are taken with food, not for the purpose of replacing tissue or yielding energy, but to add to the enjoyment of eating, to stimulate the appetite, to aid in digestion and absorption, or for some other subsidiary purpose. They include such things as the condiments (mustard, pepper, etc.), the flavors, and the stimulants (alcohol, coffee, tea, chocolate, beef-extracts). They all possess, undoubtedly, a positive nutritive or digestive value beyond contributing to the mere pleasures of the palate, but their importance is of a subordinate character as compared with the so-called alimentary principles. They may be omitted from the diet, as happens or may happen in the case of animals, without affecting injuriously the nutrition of the body, although it is probable that neither man nor the lower animals would voluntarily eat food entirely devoid of flavor.

**Stimulants.**—The well-known stimulating effect of alcohol, tea, coffee, etc., is generally attributed to a specific action on the nervous system whereby the irritability of the tissue is increased. The physiological effect of tea, coffee, and chocolate is due to the alkaloids caffeine (trimethyl-xanthin) and theobromin (dimethyl-xanthin). In small doses these substances are oxidized in the body and yield a corresponding amount of energy, but their value from this standpoint is altogether unimportant compared with their action as stimulants. Alcohol also, when not taken in too large quantities, may be oxidized in the body and furnish a not inconsiderable amount of energy. It is, however, a matter of controversy at present whether alcohol in small doses can be con-



sidered a true food-stuff, capable of replacing a corresponding amount of fats or of carbohydrates in the daily diet. The evidence is partly for and partly against such a use of alcohol. A number of observers<sup>1</sup> contend that when the body is brought into a condition of nitrogenous equilibrium on a given diet of proteids, fats, and carbohydrates, and a certain proportion of the carbohydrates or fats is then replaced by an isodynamic amount of alcohol—that is, by an amount of alcohol that on combustion would yield the same amount of heat—the body does not remain in nitrogenous equilibrium, but, on the contrary, loses in nitrogen, thus indicating that the oxidation of alcohol in the body does not protect the proteid from consumption as in the case of the non-nitrogenous food-stuffs, fats, and carbohydrates. Miura, for example, brought himself into a condition of nitrogen equilibrium upon a mixed diet. Then for a certain period a portion of the carbohydrates was omitted from the diet and its place substituted by an isodynamic amount of alcohol. The result was a loss of proteid from the body, showing that the alcohol had not protected the proteid tissue as it should have done if it acts as a food. In a third period the old diet was resumed, and after nitrogen equilibrium had again been established the same proportion of carbohydrate was omitted from the diet, but alcohol was not substituted. When the diet was poor in proteid, it was found that less proteid was lost from the body when the alcohol was omitted than when it was used, indicating that, so far from protecting the proteid of the body by its oxidation, the alcohol exercised a directly injurious effect upon proteid-consumption. Atwater,<sup>2</sup> on the contrary, as the result of elaborate experiments in which the heat production was determined calorimetrically and the body metabolism was determined also from an examination of the excreta, finds that alcohol, when substituted for the non-nitrogenous food-stuffs, does protect the proteid of the body from consumption just as the fats and carbohydrates do, and is, therefore, entitled scientifically to the designation of a food-stuff. So also Geppert and Zuntz found that alcohol in small doses caused no increase in the oxygen consumed, in spite of the fact that it was burnt in the body; the supposition in this case was that the burning of the alcohol saved some of the body material from consumption. Numerous other researches might be quoted to show that the effect of moderate quantities of alcohol upon body-metabolism is not yet satisfactorily understood. Before making any positive statements as to the details of its action it is wise, therefore, to wait until reliable experimental results have accumulated. The specific action of alcohol on the heart, stomach, and other organs has been investigated more or less completely, but the literature is too great and the results are too uncertain to permit any extended résumé to be given here. When alcohol is taken in excess it produces the familiar symptoms of intoxication, which may pass subsequently into a condition of stupor or even death, provided the quantity taken is sufficiently

<sup>1</sup> *Zeitschrift f. klin. Medicin*, 1892, Bd. xx. S. 137. See also Rosemann: *Archiv für die gesamte Physiologie*, 1899, Bd. 77, S. 405, for references.

<sup>2</sup> *American Journal of Physiology*, 1900, vol 3, p. xii.

great. So, also, the long-continued use of alcohol in large quantities is known to produce serious lesions of the stomach, liver, nerves, blood-vessels, and other organs. As has been stated before, alcohol is absorbed easily from the stomach and seems to increase the absorption of other soluble substances.<sup>1</sup> Upon the digestive action of the proteolytic and amylolytic enzymes alcohol in certain strengths has a retarding effect, but in small percentages its action is not noticeable.<sup>2</sup> Upon the secretion of saliva and gastric juice it has a distinct stimulating action,<sup>3</sup> and its action as a general stimulant to the central nervous system is indicated by its effect on the reaction time, and under certain conditions upon muscular exertion as measured by the ergograph.<sup>4</sup> The effect of alcohol upon the body evidently varies greatly with the quantity used. It may perhaps be said with safety that in small quantities it is beneficial, or at least not injurious, barring the danger of acquiring an alcohol habit, while in large quantities it is directly injurious to various tissues.

*Condiments and Flavors.*—These substances probably have a directly beneficial effect on the processes of digestion by promoting the secretion of saliva, gastric juice, etc., in addition to the important fact that they increase the palatableness of food, and hence increase the desire for food and the secretion of the gastric juice. With reference to the condiments, Brandl has shown that mustard and pepper also markedly increase the absorption of soluble products from the stomach.

*Beef-tea, Meat-extracts.*—The recent experiments of Pawlow and his co-workers (see section on Secretion) have shown that these substances have a specific value in their stimulating effect upon the gastric glands. They appear to contain substances that act as definite secretagogues toward these glands.

*Conditions Influencing Body-metabolism.*—In considering the influence of the various food-stuffs upon body-metabolism we have for the most part neglected to mention the effect of changes in the condition of the body. It goes without saying that such things as muscular work, sleep, variations in temperature, etc. have or might have an important effect upon the character and amount of the chemical changes going on in the body, and in consequence a great many elaborate investigations have been made to ascertain precisely the effect of conditions such as those mentioned upon the amount of the excretions, the production of heat in the body, and other similar points which throw light upon the nature of the metabolic processes.

*Effect of Muscular Work.*—It is a matter of common knowledge that muscular work increases the amount of food consumed, and therefore the total body-metabolism, but it has been a point in controversy whether the increased oxidations affect the proteid or the non-proteid material. According to Liebig, the source of the energy of muscular work lies in the metabolism of the proteid constituents, and with increased muscular work there should be increased de-

<sup>1</sup> Brandl: *Zeitschrift für Biologie*, 1892, Bd. 29, S. 277.

<sup>2</sup> Chittenden and Mendel: *American Journal of the Medical Sciences*, 1896.

<sup>3</sup> Chittenden, Mendel and Jackson: *American Journal of Physiology*, 1898, vol. i. p. 164.

<sup>4</sup> Schumberg: *Archiv für Physiologie*, 1899, Suppl. Bd. S. 289.



struction of proteid and an increase in the nitrogenous excretions. That the total energy of muscular work is not derived from the oxidation or metabolism of proteid alone was clearly demonstrated by the famous experiment of Fick and Wislicenus. These physiologists ascended the Faulhorn to a height of 1956 meters. Knowing the weight of his body, each could estimate how much work was done in ascending such a height. Fick's weight, for example, was 66 kilograms, therefore in climbing the mountain he performed  $66 \times 1956 = 129,096$  kilogrammeters of work. In addition, the work of the heart and the respiratory muscles, which could not be determined accurately, was estimated at 30,000 kilogrammeters. There was, moreover, a certain amount of muscular work performed in the movements of the arms and in walking upon level ground that was omitted entirely from their calculations. For seventeen hours before the ascent, during the climb of eight hours, and for six hours afterward their food was entirely non-nitrogenous, so that the urea eliminated came entirely from the proteid of the body. Nevertheless, when the urine was collected and the urea estimated it was found that the potential energy contained in the proteid destroyed was entirely insufficient to account for the work done. Although later estimates would modify somewhat the actual figures of their calculation, the margin was so great that the experiment has been accepted as showing conclusively that the total energy of muscular work does not come necessarily from the oxidation of proteid alone. Later experiments made by Voit upon a dog working in a tread-wheel and upon a man performing work while in the respiratory chamber (p. 344) gave the surprising result that not only may the energy of muscular work be far greater than the potential energy of the proteid simultaneously oxidized, but that the performance of muscular work within certain limits does not affect at all the amount of proteid metabolized in the body, since the output of urea is the same on working-days as during days of rest. Careful experiments by an English physiologist, Parkes, made upon soldiers while resting and after performing long marches showed also that there is no distinct increase in the excretion of urea after muscular exercise. It followed from these experiments that Liebig's theory as to the source of the energy of muscular work is incorrect, and that the increase in the oxidations in the body that undoubtedly occurs during muscular activity must affect only the non-proteid material, that is, the fats and carbohydrates. More recently the question was reopened by experiments made under Pflüger by Argutinsky.<sup>1</sup> In these experiments the total nitrogen excreted was determined with especial care in the sweat as well as in the urine and the feces. The muscular work done consisted in long walks and mountain-climbs. Argutinsky found that work caused a marked increase in the elimination of nitrogen, the increase extending over a period of three days, and he estimated that the additional proteid metabolized in consequence of the work was sufficient to account for most of the energy expended in performing the walks and climbs. A number of objections have been made to Argutinsky's work. It has been asserted that during his experiment he kept himself upon a

<sup>1</sup> *Pflüger's Archiv für die gesammte Physiologie*, 1890, vol. 46, p. 552.

diet deficient in non-proteid material; that if the supply of this material had been sufficient, none of the additional proteid would have been oxidized. It must be admitted, however, that the experiments of Argutinsky compel us to state the proposition above as to the relation between muscular work and proteid metabolism in a more careful way. It is necessary to modify the statement generally made to the extent of saying that muscular work causes no increase in proteid metabolism, provided the supply of non-nitrogenous food is abundant.

If now we compare the amounts of  $\text{CO}_2$  eliminated during work and during rest, it will be found that there is a very decided increase during work. In the experiments made by Pettenkofer and Voit the  $\text{CO}_2$  given off by a man during a day of muscular work was nearly double that eliminated during a resting-day. Indeed, the same fact has been observed repeatedly upon isolated muscles made to contract by artificial stimuli. Assuming, then, that muscular work causes no increase in the nitrogen excreted, but a marked increase in the  $\text{CO}_2$  eliminated, we are justified in saying that the energy of muscular work under normal conditions comes mainly, if not exclusively, from the oxidation of non-proteid material. The machine that does the work, the muscle, is *par excellence* a proteid tissue, but the normal resting metabolism of its proteid substance is not increased by the chemical changes of contraction. Or, to put it in another way, the chemical changes that give rise to the energy liberated in contraction may involve only the non-proteid material. It is interesting to remember in this connection that the consumption of glycogen, or of the sugar derived from it, is intimately connected with muscular work. The glycogen of the body in an animal deprived of food disappears much more rapidly if the animal is made to work his muscles than if he remains at rest. In an experiment by Külz upon well-fed dogs it was found that the glycogen was practically all used up in a single fasting-day during which the animals did a great deal of work. Morat and Dufourt have shown also that a muscle after prolonged contraction takes much more sugar from the blood than it did previous to the contraction, and Harley<sup>1</sup> finds that power to perform muscular work may be increased and susceptibility to fatigue be diminished by eating sugar in quantities. It is, in fact, generally agreed that glycogen is used up in muscle-contractions, but the way in which the destruction of the glycogen is effected is not definitely known. After the glycogen has been consumed it is probable that the other constituents of the body, the fats and the proteids, are called upon to furnish the necessary energy. For this reason we should expect, in a person performing excessive muscular work, that there would be an increased destruction of proteid when the supply of non-proteid food is insufficient.

*Metabolism during Sleep.*—It has been shown that during sleep there is no marked diminution of the nitrogen excreted, and therefore no distinct decrease in the proteid metabolism; on the contrary, the  $\text{CO}_2$  eliminated and the oxygen absorbed are unquestionably diminished. This latter fact finds its

<sup>1</sup> *Journal of Physiology*, 1894, vol. xvi. p. 97.



simplest explanation in the supposition that the muscles are less active during sleep. The muscles do less work in the way of contractions, and, in addition, probably suffer a diminution in tonicity which also affects their total metabolism.

*Effect of Variations in Temperature.*—In warm-blooded animals variations of outside temperature within ordinary limits do not affect the body-temperature. A full account of the means by which this regulation is effected will be found in the section upon Animal Heat. So long as the temperature of the body remains constant, it has been found that a fall of outside temperature may increase the oxidation of non-proteid material in the body, the increase being in a general way proportional to the fall in temperature. That the increased oxidation affects the non-proteid constituents is shown by the fact that the urea remains unchanged in quantity, other conditions being the same, while the oxygen-consumption and the  $\text{CO}_2$ -elimination are increased. This effect of temperature upon the body-metabolism is due mainly to a reflex stimulation of the motor nerves to the muscles. The temperature-nerves of the skin are affected by the fall in outside temperature, and bring about reflexly an increased or a diminished innervation of the muscles of the body. Indeed, it is stated<sup>1</sup> that unless the lowering of the temperature is sufficient to cause shivering or muscular tension no increase in the  $\text{CO}_2$ -excretion results. This fact suffices to explain, therefore, the physiological value of shivering and muscular restlessness when the outside temperature is low. The fact that variations in outside temperature affect only the consumption of non-proteid material falls in, therefore, with the conception of the nature of the metabolism of muscle in activity, given above. When the means of regulating the body-temperature break down from too long an exposure to excessively low or excessively high temperatures, the total body-metabolism, proteid as well as non-proteid, increases with a rise in body-temperature and decreases with a fall in temperature. In fevers arising from pathological causes it has been shown that there is also an increased production of urea as well as of  $\text{CO}_2$ .

*Effect of Starvation.*—A starving animal must live upon the material present in its body. This material consists of the fat stored up, the circulating and tissue proteid, and the glycogen. The latter, which is present in comparatively small quantities, is quickly used, disappearing more or less rapidly according to the extent of muscular movements made, although in any case it practically vanishes in a few days. Thereafter the animal lives on its own proteid and fat, and if the starvation is continued to a fatal termination the body becomes correspondingly emaciated. Examination of the several tissues in animals starved to death has brought out some interesting facts. Voit took two cats of nearly equal weight, fed them equally for ten days, and then killed one to serve as a standard of comparison and starved the other for thirteen days: the latter animal lost 1017 grams in weight, and the loss was divided as follows among the different organs:

<sup>1</sup> Johansson: *Skandinavisches Archiv für Physiologie*, 1897, Bd. vii. S. 123.

	Supposed wt. of organs before starvation.	Actual loss of organs in grams.	Loss to each 100 grams of fresh organ (percentage loss).
Bone . . . . .	393.4	54.7	13.9
Muscle . . . . .	1408.4	429.4	30.5
Liver . . . . .	91.9	49.4	53.7
Kidney . . . . .	25.1	6.5	25.9
Spleen . . . . .	8.7	5.8	66.7
Pancreas . . . . .	6.5	1.1	17.0
Testes . . . . .	2.5	1.0	40.0
Lungs . . . . .	15.8	2.8	17.7
Heart . . . . .	11.5	0.3	2.6
Intestines . . . . .	118.0	20.9	18.0
Brain and cord . . . . .	40.7	1.3	3.2
Skin and hair . . . . .	432.8	89.3	20.6
Fat . . . . .	275.4	267.2	97.0
Blood . . . . .	138.5	37.3	27.0
Remainder . . . . .	136.0	50.0	36.8

According to these results, the greatest absolute loss was in the muscles (429 grams), while the greatest percentage loss was in the fat (97 per cent.), which had practically disappeared from the body. It is very significant that the central nervous system and the heart, organs which we may suppose were in continual activity, suffered practically no loss of weight: they had lived at the expense of the other tissues. We must suppose that in a starving animal the fat and the proteid material, particularly that of the voluntary muscles, pass into solution in the blood, and are then used to nourish the tissues generally and to supply the heat necessary to maintain the body-temperature. Examination of the excreta in starving animals has shown that a greater quantity of proteid is destroyed during the first day or two than in the subsequent days. This fact is explained on the supposition that the body is at first richly supplied with "circulating proteid" derived from its previous food, and that after this is metabolized the animal lives entirely, so far as proteid-consumption is concerned, upon its "tissue proteid." If the animal remains quiet during starvation, the amount of nitrogen excreted daily soon reaches a nearly constant minimum, showing that a practically constant amount of proteid (together with fat) is consumed daily to furnish body-heat, and probably to repair tissue waste in the active organs, such as the heart. Shortly before death from starvation the daily amount of proteid consumed may increase, as shown by the larger amount of nitrogen eliminated. This fact is explained by assuming that the body fat is then exhausted and the animal's metabolism is confined to the tissue proteids alone. The general fact that the loss of proteid is greatest during the first one or two days of starvation has been confirmed recently upon men, in a number of interesting experiments made upon professional fasters. For the numerous details as to loss of weight, variations of temperature, etc., carefully recorded in these latter experiments, reference must be made to original sources.<sup>1</sup> It may be added, in conclusion, that the fatter the body is to begin with, the longer will

<sup>1</sup> Virchow's *Archiv*, Bd. 131, supplement, 1893, and Luciani, *Das Hungern*, 1890.



starvation be endured, and if water is consumed freely the evil effects of starvation, as well as the disagreeable sensations of hunger, are very much reduced.

**Potential Energy of Food.**—The chemical changes occurring in the body are accompanied by a transformation of chemical energy to different forms—for example, to heat, electricity, and mechanical work. By far the most of this energy takes the form, directly or indirectly, of heat. Even when the muscles are apparently at rest we know that they are undergoing chemical changes which give rise to heat. When a muscle contracts, the greater part (four-fifths) of the energy liberated by the chemical change takes the form of heat; a much smaller part (about one-fifth as a maximum) may perform mechanical work, which in turn, as in the case of the respiratory muscles and the heart, may be converted to heat within the body. Roughly speaking, an adult man gives off from his body in the course of twenty-four hours about 2,400,000 calories of heat (1 calorie = the heat necessary to raise 1 cubic centimeter of water  $1^{\circ}$  C.). This supply of heat is derived from the metabolism or physiological oxidation of the proteids, the fats, and the carbohydrates that we take into the body in our food. By means of the oxygen absorbed through the lungs these substances are burnt, with the formation of  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ , and urea or some similar nitrogenous waste product. In the long run, then, the source of body-energy is found in the potential energy contained in our food. Our energy-yielding foods—proteids, fats, and carbohydrates—are more or less complex bodies that are built up originally by plant organisms with the aid of solar energy; when they are burnt or otherwise destroyed, with the formation of simpler bodies (such as  $\text{CO}_2$  or  $\text{H}_2\text{O}$ ), their so-called potential energy is liberated in the form of heat, and this is what occurs in the body. From the standpoint of the law of conservation of energy it is easy to understand that the amount of available energy in any food-stuff may be determined by burning it outside the body and measuring the quantity of heat liberated. If a gram of sugar is burnt, it is converted to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  and a certain quantity of heat is liberated; if the same gram of sugar had been taken into the body, it would eventually have been reduced to the form of  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , and the total quantity of heat liberated would have been the same as in the combustion outside the body, although the destruction of the sugar in the body may not be a direct, but an indirect, oxidation: that is, the oxygen may first be combined with sugar and other food-stuffs to form a complex molecule which afterward dissociates into simpler compounds similar to those obtained by direct oxidation, or there may be first a dissociation or cleavage followed by oxidation of the dissociation products. In determining the total energy given to the body we need only consider the form in which a substance enters the body and the form in which it is finally eliminated. In the case of proteids the combustion in the body is not so complete as it is outside; the chief final products are  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ , and urea. The urea, however, still contains potential energy which may be liberated by combustion, and in determining the energy of proteid available to the body, that which is lost in the urea must be deducted. As a matter of fact, it is possible that the proteid in the body is completely oxidized to  $\text{CO}_2$ ,

$H_2O$ , and  $NH_3$ ; but, since the  $NH_3$  in this case is recombined to form an ammonium compound, and this in turn is converted into urea, the additional energy liberated in the first combustion is balanced by that absorbed in the synthetic production of the urea. The potential energy of the fats, carbohydrates, and proteids can be determined by combustion outside the body; the energy liberated is measured in terms of heat by some form of calorimeter, and the quantity of heat so obtained, expressed in calories, is known usually as the "combustion equivalent." To be perfectly accurate, each particular form of fat, proteid, etc. should be burnt and its energy be determined, but usually average figures are employed, as the amount of heat given off by the different varieties of any one food-stuff—proteids, for example—does not vary greatly. According to Stohmann, 1 gram of beef deprived of fat = 5641 calories, while 1 gram of veal gives 5663 calories. For muscle extracted with water, Rubner obtained the following figures: 1 gram = 5778 calories. The combustion equivalent of urea (Rubner) is 2523 calories. Since 1 gram of proteid yields about one-third of a gram of urea, we should deduct 841 calories from the combustion equivalent of one gram of proteid to get its available energy to the body: 5778—841=4937 calories. Practically, however, this value is found to be too high. Direct determinations upon the body in a calorimeter gave to Rubner the following values, which seem to be generally adopted by workers in this field: 1 gram of proteid = 4100 calories, 1 gram of fat = 9300 calories, 1 gram of carbohydrate = 4100 calories. Weight for weight, fat contains the most energy, and, as we know, in cold weather and in cold climates the proportion of fat in the food is increased. In dietetics, however, the use of fat is limited by the difficulty attending its digestion and absorption as compared with carbohydrates. Fats and carbohydrates have the same general nutritive value to the body: they serve to supply energy. Since the amount of potential energy contained in each of these substances may be determined accurately by means of its combustion equivalent, it would seem probable that they might be mutually interchangeable in dietetics in the ratio of their combustion equivalents. Such, in fact, is the case. The ratio of interchange is known as the "isodynamic equivalent," and it is given usually as 1 : 2.4 or 2.2; that is, fats may replace over twice their weight of carbohydrate in the diet. It follows from the general principles just stated that if we wished to know the amount of heat produced in the body in a given time, say twenty-four hours, we might ascertain it in one of two ways: In the first place, the animal might be placed in a calorimeter and the heat given off in twenty-four hours be measured directly. This method, which is that of direct calorimetry, is described more completely in the section treating of Animal Heat. Secondly, one might feed the animal upon a diet containing known quantities of proteid, fats, and carbohydrates, and by collecting the total N and C excreta determine how much of each of these had been destroyed in the body. Knowing the combustion equivalent of each, the total quantity of heat liberated in the body could be ascertained. This latter method is known as indirect calorimetry. The two methods, if applied simultaneously to the same animal, should give identical results. It is very interesting to know that an experiment of this character



has been successfully performed by Rubner;<sup>1</sup> his experiments were made with the greatest accuracy and with careful attention to all the possible sources of error, and it was found that the quantities of heat as determined by the two methods agreed to within less than 0.5 per cent. These experiments are noteworthy because they furnish us with the first successful experimental demonstration of the accuracy of the general principles, stated above, upon which the available energy of foods is calculated.

**Dietetics.**—The subject of the proper nourishment of individuals or collections of individuals—armies, inmates of hospitals, asylums, prisons, etc.—is treated usually in books upon hygiene, to which the reader is referred for practical details. The general principles of dieting have been obtained, however, from experimental work upon the nutrition of animals. These principles have been stated more or less completely in the foregoing pages, but some additional facts of importance may be referred to conveniently at this point. In a healthy adult who has attained his maximum weight and size the main object of a diet is to furnish sufficient nitrogenous and non-nitrogenous food-stuffs, together with salts and water, to maintain the body in equilibrium—that is, to prevent loss of proteid tissue, fat, etc. In speaking of the nutritive value of the food-stuffs it was shown that in carnivora (dogs) this condition of equilibrium may be maintained upon proteid food alone, putting aside all consideration of salts and water, or upon proteids and fats, or upon proteids and carbohydrates, or upon proteids, fats, and carbohydrates. When proteids alone are used, the quantity must be increased far above that necessary in the case of a mixed diet, and it is doubtful whether, in the case of man or the herbivora, a healthy nutritive condition could be maintained long upon such a diet, owing to the largely increased demand upon the power of the alimentary canal to digest and absorb proteids, to the greater labor thrown on the kidneys, etc. The experience of mankind, as well as the results of experimental investigation, shows that the healthy diet is one composed of proteids, fats, and carbohydrates. The proportion in which the fats and the carbohydrates should be taken—and, to a certain extent, this is true also of the proteids—may be varied within comparatively wide limits, in accordance with the law of “isodynamic equivalents,” provided that the total amount of potential energy represented in the food does not fall below a certain amount, on the average about 40,000 calories per kilo. of body weight. This is illustrated by the following “average diets” calculated by different physiologists to indicate the average amount of food-stuffs required by an adult man under normal conditions of life:

Average Diets.

	Moleschott.	Ranke.	Volt.	Forster.	Atwater.
Proteid . . . . .	130 grams.	100 grams.	118 grams.	131 grams.	125 grams.
Fats . . . . .	40 “	100 “	56 “	68 “	125 “
Carbohydrates . . . .	550 “	240 “	500 “	494 “	400 “

<sup>1</sup> *Zeitschrift für Biologie*, 1893, Bd. xxx. S. 73.

In Voit's diet, which is the one usually taken to represent the daily needs of the body, it will be noticed that the ratio of the nitrogenous to the non-nitrogenous food-stuffs is about as 1 : 5, and basing the estimate upon a man weighing 70-75 kilos., 118 grams of proteid per day would represent a consumption of proteid equal to 1.3 to 1.7 grams per kilo. of weight. Siven<sup>1</sup> has recently attempted to show that this proportion of proteid in food is unnecessarily high. In some experiments upon himself he was able to reduce his daily proteid food to about 0.2 gram per kilo. of body weight and still maintain his body in N-equilibrium, provided the non-proteid portions of his diet were so increased that the total energy of his daily diet remained unchanged. Whether or not so high an amount of proteid per day as 118 grams is most beneficial to the body, under normal conditions of moderate labor, is perhaps an open question. It seems certain that for short periods at least the average individual can keep his body in equilibrium on much smaller amounts. It must be remembered, in regard to these diets, that the amounts of food-stuffs given refer to the dry material: 118 grams of proteid do not mean 118 grams of lean meat, for example, since lean meat (flesh) contains a large proportion of water. Tables of analyses of food (one of which is given on page 278) enable us to determine for each particular article of food the proportion of dry food-stuffs contained in it, and in how great quantities it must be taken to furnish the requisite amount of proteid, fats, or carbohydrates. There is, however, still another practical consideration that must be taken into account in estimating the nutritive value of articles of food from the analyses of their composition, and that is the extent to which each food-stuff in each article of food is capable of being digested and absorbed. Practical experience has shown that proteids in certain articles of food can be digested and absorbed nearly completely when not fed in excess, while in other foods only a certain percentage of the proteid is absorbed under the most favorable conditions. This difference in usability of the food-stuffs in various foods is most marked in the case of proteids, but it occurs also with the fats and the carbohydrates. Facts of this kind cannot be determined by mere analysis of the foods; they must be obtained from actual feeding experiments upon man or the lower animals. It has usually been stated by those who have worked in this field that the proteids of meats are more completely utilized than those of vegetables. But it is possible that as a generalization this statement is too sweeping, and rests upon the erroneous assumption that the nitrogen in feces represents chiefly undigested proteid. Prausnitz<sup>2</sup> and others have given reasons for believing that the nitrogen in the feces is derived mainly from the intestinal secretions, and that vegetable foods that do not contain much indigestible material, such as rice and bread, are practically completely digested and absorbed in the intestines, their proteids, therefore, being utilized as completely as in the case of meats. Munk<sup>3</sup> gives an inter-

<sup>1</sup> *Skandinavisches Archiv für Physiologie*, 1899, Bd. 10, S. 91.

<sup>2</sup> *Zeitschrift für Biologie*, 1897, Bd. 35, S. 335.

<sup>3</sup> *Weyl's Handbuch der Hygiene*, 1893, Bd. iii. Theil i. S. 69.



esting table showing how much of certain familiar articles of food would be necessary, if taken alone, to supply the requisite daily amount of proteid or non-proteid food; his estimates are based upon the percentage composition of the foods and upon experimental data showing the extent of absorption of the food-stuffs in each food. In this table he supposes that the daily diet should contain 110 grams of proteid = 17.5 grams of N, and non-proteids sufficient to contain 270 grams of C:

	For 110 grams proteid (17.5 grams N).	For 270 grams C
Milk . . . . .	2900 grams.	3800 grams.
Meat (lean) . . . . .	540 "	2000 "
Hen's eggs . . . . .	18 eggs.	37 eggs.
Wheat flour . . . . .	800 grams.	670 grams.
Wheat bread . . . . .	1650 "	1000 "
Rye bread . . . . .	1900 "	1100 "
Rice . . . . .	1870 "	750 "
Corn . . . . .	990 "	660 "
Peas . . . . .	520 "	750 "
Potatoes . . . . .	4500 "	2550 "

As Munk points out, this table shows that any single food, if taken in quantities sufficient to supply the nitrogen, would give too much or too little C, and the reverse; those animal foods which, in certain amounts, supply the nitrogen needed furnish only from one-quarter to two-thirds of the necessary amount of C. To live for a stated period upon a single article of food—a diet sometimes recommended to reduce obesity—means, then, an insufficient quantity of either N or C and a consequent loss of body-weight. Such a method of dieting amounts practically to a partial starvation. In practical dieting we are accustomed to get our supply of proteids, fats, and carbohydrates from both vegetable and animal foods. To illustrate this fact by an actual case, in which the food was carefully analyzed, an experimenter (Krummacher) weighing 67 kilograms records that he kept himself in N equilibrium upon a diet in which the proteid was distributed as follows:

300 grams meat	=	63.08 grams proteid	=	9.78 grams N.
666.3 c.c. milk	=	18.74 " "	=	2.905 " "
100 grams rice	=	7.74 " "	=	1.2 " "
100 " bread	=	11.32 " "	=	1.755 " "
500 c.c. wine	=	1.17 " "	=	0.182 " "
		102.05 " "	=	15.868 " "

For a person in health and leading an active normal life, appetite and experience seem to be safe and sufficient guides by which to control the diet; but in conditions of disease, in regulating the diet of children and of collections of individuals, scientific dieting, if one may use the phrase, has accomplished much, and will be of greater service as our knowledge of the physiology of nutrition increases.

## VI. MOVEMENTS OF THE ALIMENTARY CANAL, BLADDER, AND URETER.

### PLAIN MUSCLE-TISSUE.

THE movements of the alimentary canal and the organs concerned in micturition are effected for the most part through the agency of plain muscle-tissue. The general properties of this tissue will be referred to in the section upon the Physiology of Muscle and Nerve, but it seems appropriate in this connection to call attention to some few points in its general physiology and histology, inasmuch as the character of the movements to be described depends so much upon the fundamental properties exhibited by this variety of muscle-tissue. Plain muscle as it is found in the walls of the abdominal and pelvic viscera is composed of masses of minute spindle-shaped cells whose size is said to vary from 22 to 560  $\mu$  in length and from 4 to 22  $\mu$  in width, the average size, according to Kölliker, being 100 to 200  $\mu$  in length and 4 to 6  $\mu$  in width. Each cell has an elongated nucleus, and its cytoplasm shows a longitudinal fibrillation. Cross striation, such as occurs in cardiac and striped muscle, is absent. These cells are united into more or less distinct bundles or fibres, which run in a definite direction corresponding to the long axes of the cells. The bundles of cells are united to form flat sheets of muscle of varying thicknesses, which constitute part of the walls of the viscera and are distinguished usually as longitudinal and circular muscle-coats according as the cells and bundles of cells have a direction with or at right angles to the long axis of the viscus. The constituent cells are united to one another by cement-substance, and according to several observers<sup>1</sup> there is a direct protoplasmic continuity between neighboring cells—an anatomical fact of interest, since it makes possible the conduction of a wave of contraction directly from one cell to another. Plain muscle-tissue, in some organs at least, *e. g.* the stomach, intestines, bladder, and arteries, is under the control of motor nerves. There must be, therefore, some connection between the nerve-fibres and the muscle-tissue. The nature of this connection is not definitely established; according to Miller,<sup>2</sup> the nerve-fibres terminate eventually in fine nerve-fibrils that run in the cement-substance between the cells and send off small branches that end in a swelling applied directly to the muscle-cell. Berkley<sup>3</sup> finds a similar

<sup>1</sup> See Boheman: *Anatomischer Anzeiger*, 1894, Bd. 10, No. 10.

<sup>2</sup> *Archiv für mikroskopische Anatomie*, 1892, Bd. 40.

<sup>3</sup> *Anatomischer Anzeiger*, 1893, Bd. 8.



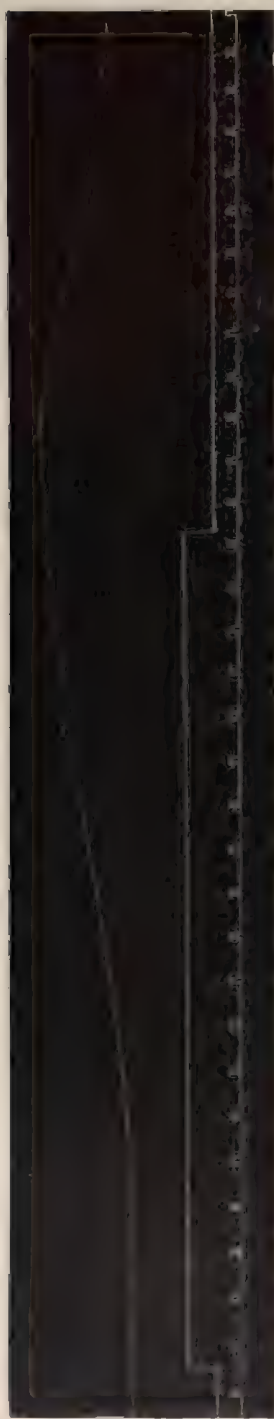


FIG. 68.—Contraction of a strip of plain muscle from the stomach of a terrapin. The bottom line gives the time-record in seconds; the middle line shows the time of application of the stimulus, a tetanizing current from an induction coil; the upper line is the curve recorded by the contracting muscle.

ending of the nerves, and in addition describes in the muscularis mucosæ of the intestine a large globular end-organ which he considers as a motor plate.

Perhaps the most striking physiological peculiarity of plain muscle, as compared with the more familiar striated muscle, is the sluggishness of its contractions. Plain muscle, like striated muscle, is independently irritable. Various forms of artificial stimuli, such as electrical currents, mechanical, chemical, and thermal stimuli, may cause the tissue to contract when directly applied to it, but the contraction in all cases is characterized by the slowness with which it develops. There is a long latent period, a gradual shortening which may persist for some time after the stimulus ceases to act, and a slow relaxation. These features are represented in the curve shown in Figure 68, which it is instructive to compare with the typical curve of a striated muscle (Vol. II.). The slowness of the contraction of plain muscle seems to depend upon the absence of cross striation. Striped muscle as found in various animals or in different muscles of the same animal—*e. g.* the pale and red muscles of the rabbit—differs greatly in the rapidity of its contraction, and it has been shown that the more perfect the cross striation the more rapid is the contraction. The cross striation, in other words, is the expression of a mechanism or structure adapted to quick contractions and relaxations, and the relatively great slowness of movement in the plain muscle seems to result from the absence of this particular structure. It should be added, however, that plain muscle in different parts of the body exhibits considerable variation in the rapidity with which it contracts under stimulation, the ciliary muscle of the eyeball, for example, being able to react more rapidly than the muscles of the intestines. The gentle prolonged contraction of the plain muscle is admirably adapted to its function in the intestine of moving the food-contents along the canal with sufficient slowness to permit normal digestion and absorption. Like the striated muscle, and unlike the cardiac muscle, plain muscle is capable of

giving submaximal as well as maximal contractions; with increased strength of stimulation the amount of the shortening increases until a maximum is reached. This fact may be observed not only upon isolated strips of muscle from the stomach, but may be seen also in the different degrees of contraction exhibited by the intestinal musculature as a whole when acted upon by various stimuli.

In his researches upon the movements of the ureter Engelmann<sup>1</sup> showed that a stimulus applied to the organ at any point caused a contraction that, starting from the point stimulated, might spread for some distance in either direction. Engelmann interprets this to mean that the contraction wave in the case of the ureter is propagated directly from cell to cell, and this possibility is supported by the fact, before referred to, that there is direct protoplasmic continuity between adjoining cells. This passage of a contraction wave from cell to cell has, in fact, often been quoted as a peculiarity of plain muscle-tissue. In the case of the ureter the fact seems to be established, but in the intestines, where there is a rich intrinsic supply of nerve-ganglia, it is not possible to demonstrate clearly that the same property is exhibited. The wave of contraction in the intestine following artificial stimulation is, according to most observers, usually localized at the point stimulated or is propagated in only one direction, and these facts are difficult to reconcile with the hypothesis that each cell may transmit its condition of activity directly to neighboring cells. Upon the plain muscle of the ureter Engelmann was able to show also an interesting resemblance to cardiac muscle, in the fact that each contraction is followed by a temporary diminution in irritability and conductivity; but this important property, which in the case of the heart has been so useful in explaining the rhythmic nature of its contractions, has not been demonstrated for all varieties of plain muscle occurring in the body.

A general property of plain muscle that is of great significance in explaining the functional activity of this tissue is exhibited in the phenomenon of "tone." By tone or tonic activity as applied to muscle-tissue is meant a condition of continuous contraction or shortening that persists for long periods and may be slowly increased or decreased by various conditions affecting the muscle. Both striated and cardiac muscle exhibit tone, and in the latter at least the condition may be independent of any inflow of nerve-impulses from the extrinsic nerves. Plain muscle exhibits the property in a marked degree. The muscular coats of the alimentary canal, the blood-vessels, the bladder, etc., are usually found under normal circumstances in a condition of tone that varies from time to time and differs from an ordinary visible contraction in the slowness with which it develops and in its persistence for long periods. Such conditions as the reaction of the blood, for example, are known to alter greatly the tone of the blood-vessels, a less alkaline reaction than normal causing relaxation, while an increase in alkalinity favors the development of tone. Tone may also be increased or diminished by the action of motor or

<sup>1</sup> *Pflüger's Archiv für die gesammte Physiologie*, 1869, Bd. 2, S. 243.



inhibitory nerve-fibres, but the precise relationship between the changes underlying the development of tone and those leading to the formation of an ordinary contraction has not been satisfactorily determined.

The mode of contraction of the plain muscle in the walls of some of the viscera, especially the intestine and ureter, is so characteristic as to be given the special name of peristalsis. By peristalsis, or vermicular contraction as it is sometimes called, is meant a contraction which, beginning at any point in the wall of a tubular viscus, is propagated along the length of the tube in the form of a wave, each part of the tube as the wave reaches it passing slowly into contraction until the maximum is reached, and then gradually relaxing. In viscera like the intestine, in which two muscular coats are present, the longitudinal and the circular, the peristalsis may involve both layers, either simultaneously or successively, but the striking feature observed when watching the movement is the contraction of the circular coat. The contraction of this coat causes a visible constriction of the tube that may be followed by the eye as it passes onward.

#### MASTICATION.

Mastication is an entirely voluntary act. The articulation of the mandibles with the skull permits a variety of movements; the jaw may be raised and lowered, may be projected and retracted, or may be moved from side to side, or various combinations of these different directions of movement may be effected. The muscles concerned in these movements and their innervation are described as follows: The masseter, temporal and internal pterygoids raise the jaw; these muscles are innervated through the inferior maxillary division of the trigeminal. The jaw is depressed mainly by the action of the digastric muscle, assisted in some cases by the mylo-hyoid and the genio-hyoid. The two former receive motor-fibres from the inferior maxillary division of the fifth cranial, the last from a branch of the hypoglossal. The lateral movements of the jaws are produced by the external pterygoids, when acting separately. Simultaneous contraction of these muscles on both sides causes projection of the lower jaw. In this latter case forcible retraction of the jaw is produced by the contraction of a part of the temporal muscle. The external pterygoids also receive their motor fibres from the fifth cranial nerve, through its inferior maxillary division. The grinding movements commonly used in masticating the food between the molar teeth are produced by a combination of the action of the external pterygoids, the elevators, and perhaps the depressors. At the same time the movements of the tongue and of the muscles of the cheeks and lips serve to keep the food properly placed for the action of the teeth, and to gather it into position for the act of swallowing.

#### DEGLUTITION.

The act of swallowing is a complicated reflex movement which may be initiated voluntarily, but is for the most part completed quite independently

of the will. The classical description of the act given by Magendie divides it into three stages, corresponding to the three anatomical regions, the mouth, pharynx and œsophagus, through which the swallowed morsel passes on its way to the stomach. The first stage consists in the passage of the bolus of food through the isthmus of the fauces—that is, the opening lying between the ridges formed by the palato-glossi muscles, the so-called anterior pillars of the fauces. This part of the act is usually ascribed to the movements of the tongue itself. The bolus of food lying upon its upper surface is forced backward by the elevation of the tongue against the soft palate from the tip toward the base. This portion of the movement may be regarded as voluntary, to the extent at least of manipulating the food into its proper position on the dorsum of the tongue, although it is open to doubt whether the entire movement is usually effected by a voluntary act. Under normal conditions the presence of moist food upon the tongue seems essential to the complete execution of the act; and an attempt to make the movement with very dry material upon the tongue is either not successful or is performed with difficulty. The second act comprises the passage of the bolus from the isthmus of the fauces to the œsophagus—that is, its transit through the pharynx. The pharynx being a common passage for the air and the food, it is important that this part of the act should be consummated quickly. According to the usual description the motor power driving the bolus downward through the pharynx is derived from the contraction of the pharyngeal muscles, particularly the constrictors, which contract from above downward and drive the food into the œsophagus. Simultaneously, however, a number of other muscles are brought into action, the general effect of which is to shut off the nasal and laryngeal openings and thus prevent the entrance of food into the corresponding cavities. The whole reflex is therefore an excellent example of a finely co-ordinated movement.

The following events are described: The mouth cavity is shut off by the position of the tongue against the palate and by the contraction of the muscles of the anterior pillars of the fauces. The opening into the nasal cavity is closed by the elevation of the soft palate (action of the levator palati and tensor palati muscles) and the contraction of the posterior pillars of the fauces (palato-pharyngei muscles) and the elevation of the uvula (azygos uvulae muscle). The soft palate, uvula, and posterior pillars thus form a sloping surface shutting off the nasal chamber and facilitating the passage of the food backward into the pharynx where the constrictor muscles may act upon it. The respiratory opening into the larynx is closed by the adduction of the vocal cords (lateral crico-arytenoids and constrictors of the glottis) and by the elevation of the entire larynx and a depression, in part mechanical, of the epiglottis over the larynx (action of the thyro-hyoids, digastrics, genio-hyoids, and mylo-hyoids and the muscles in the aryteno-epiglottidean folds). The movements of the epiglottis during this stage of swallowing have been much discussed. The usual view is that it is pressed down upon the laryngeal orifice like the lid of a box and thus effectually protects the respiratory passage. It has been shown, however, that removal of the epiglottis does not prevent normal swallowing,



and Stuart and McCormick<sup>1</sup> have reported the case of a man in whom part of the pharynx had been permanently removed by surgical operation and in whom the epiglottis could be seen during the act of swallowing. In this individual, according to their observations, the epiglottis was not folded back during swallowing, but remained erect. Later observations by Kanthack and Anderson,<sup>2</sup> made partly upon themselves and partly upon the lower animals, tend, on the contrary, to support the older view. They state that in normal individuals the movement of the epiglottis backward during swallowing may be felt by simply passing the finger back into the pharynx until it comes into contact with the epiglottis. At the beginning of the movement there is also a contraction of the longitudinal muscles of the pharynx which tends to pull the pharyngeal walls toward the bolus of food while, as has been said, the nearly simultaneous contraction of the constrictors presses upon the food and forces it downward. The food is thus brought quickly into the opening of the œsophagus and the third stage commences.

The transit of the food through the œsophagus is effected by the action of its intrinsic musculature. The muscular coat is arranged in two layers, an external longitudinal and an internal circular. These are composed of plain muscle-tissue in the lower third or two-thirds of the œsophagus, but in most mammals the upper third or more contains striated muscular tissue. The chief factor in the transportation of the bolus through the œsophagus has been supposed to consist in the contraction of the circular muscle. This contraction begins at the pharyngeal opening of the œsophagus and passes downward in the form of a wave, peristaltic contraction, which moves rapidly in the upper segment where the musculature is striated, and more slowly in the lower segments in accordance with the physiological characteristics of plain muscle. The result of this movement would naturally be to force the food onward to the stomach. The longitudinal muscles of the œsophagus are without doubt brought into action at the same time, but in this as in other cases of peristalsis in tubular viscera it is not perfectly clear how they co-operate in producing the onward movement. It may be that their contraction slightly precedes that of the circular muscle, and thus tends to dilate the tube and to bring it forward over the bolus. At the opening of the œsophagus into the stomach, the cardiac orifice, the circular fibres of the œsophagus function as a sphincter which is normally in a condition of tone, particularly when the stomach contains food, and thus shuts off the cavity of the stomach from the œsophagus. In swallowing, however, the advancing peristaltic wave has sufficient force to overcome the tonicity of the sphincter, or possibly there is at this moment a reflex inhibition of the sphincter. In either case the result is that the food is forced through the narrow opening into the stomach with sufficient energy to give rise to a sound that may be heard by auscultation over this region.<sup>3</sup> According to measurements by Kronecker and Meltzer the entrance of the

<sup>1</sup> *Journal of Anatomy and Physiology*, 1892.

<sup>2</sup> *Journal of Physiology*, 1893, vol. xiv. p. 154.

<sup>3</sup> See Meltzer. *Centralblatt für die med. Wissenschaften*, 1881, No. 1.

food into the stomach occurs in man about six seconds after the beginning of the act of swallowing.

**Kronecker-Meltzer Theory of Deglutition.**—The usual view of the mechanism of swallowing has been seriously modified by Kronecker and Meltzer.<sup>1</sup> The experiments of these observers seem to be so conclusive that we must believe that in the main their explanation of the process is correct. According to their view the chief factor in forcing soft or liquid food through the pharynx and œsophagus is the sharp and strong contraction of the mylo-hyoid muscles. The bolus of food lies upon the dorsum of the tongue and by the pressure of the tip of the tongue against the palate it is shut off from the front part of the mouth-cavity. The mylo-hyoids now contract, and the bolus of food is put under high pressure and is shot in the direction of least resistance—namely, through the pharynx and œsophagus. This effect is aided by the simultaneous contractions of the hyoglossi muscles, which tend to still further increase the pressure upon the food by moving the tongue backward and downward. This same movement of the tongue suffices also to depress the epiglottis over the larynx, and thus protect the respiratory opening. By means of small rubber bags connected with recording tambours, which were placed in the pharynx and at different levels in the œsophagus, they were able to demonstrate the rapid spirting of the food through the whole length of pharynx and into the œsophagus, the time elapsing between the beginning of the swallowing movement and the arrival of the food at the lower end of the œsophagus being not more than 0.1 second. The contraction of the constrictors of the pharynx and the peristaltic wave along the œsophagus, according to this view, normally follow after the food has been swallowed, and may be regarded as a movement in reserve which is useful in removing adherent fragments along the deglutition passage, or possibly, in cases of the failure of the first swallowing act from any cause—as may result, for instance, in swallowing food too dry or too solid—serves actually to push the bolus downward, although at a much slower rate. From auscultation of the deglutition sound which ensues when the food enters the stomach through the cardia, Kronecker and Meltzer believe that usually the swallowed food after reaching the lower portion of the œsophagus does not enter the stomach until the subsequent peristaltic wave of the œsophagus, which reaches the same point in about six seconds after the beginning of the act of swallowing, forces it through. According to Cannon and Moser,<sup>2</sup> the rapid projection of food into the deeper part of the œsophagus occurs only with liquids. When the food is solid or semisolid peristalsis is required to move the bolus through the œsophagus. Kronecker and Meltzer were able to determine by their method of recording that the human œsophagus contracts apparently in three successive segments. The first of these comprises about six centimeters in the neck region, and its contraction begins about 1 or 1.2 seconds after the

<sup>1</sup> *Archiv für Physiologie*, 1883, Suppl. Bd., S. 328; also *Journal of Experimental Medicine*, 1897, vol. ii, p. 453.

<sup>2</sup> *American Journal of Physiology*, 1898, vol. i, p. 435.



beginning of swallowing and is comparatively short, lasting 2 seconds, corresponding to the striated character of the muscle. The second segment covers about ten centimeters of the upper thoracic portion of the œsophagus; its contraction begins about 1.8 seconds after the beginning of the contraction of the first segment, and is longer, lasting 6 to 7 seconds. The third segment includes the remainder of the œsophagus; its contraction begins about 3 seconds after the contraction of the second segment, and lasts a much longer time, about 9–10 seconds. These figures apply, of course, to a single act of swallowing. It will be seen that according to these authors the swallowing reflex consists essentially in the successive contractions of five muscular segments or bands—namely, the mylo-hyoids, the constrictors of the pharynx, and the three segments of the œsophagus described. The time elapsing between the contractions of these successive parts was determined as follows:

From the beginning of the contraction of the mylo-hyoids to that of the constrictors of the pharynx . . . . .	0.3 second.
From the beginning of the contraction of the constrictors to that of the first œsophageal segment . . . . .	0.9 "
Between the first and second œsophageal segments . . . . .	1.8 seconds.
" " second and third " " . . . . .	3.0 "

The total time before the wave of contraction reaches the stomach would be therefore, as has been stated, about six seconds. When a second act of swallowing is made within six seconds of the first swallow it causes an inhibition, apparently by a reflex effect upon the deglutition centre, of the part of the tract which has not yet entered into contraction, so that the peristaltic wave does not reach the lower end of the œsophagus until six seconds after the second act of swallowing.

**Nervous Control of Deglutition.**—The entire act of swallowing, as has been said before, is essentially a reflex act. Even the comparatively simple wave of contraction that sweeps over the œsophagus is apparently due to a reflex nervous stimulation, and is not a simple conduction of contraction from one portion of the tube to another. This fact was demonstrated by the experiments of Mosso,<sup>1</sup> who found that after removal of an entire segment from the œsophagus the peristaltic wave passed to the portion of the œsophagus left on the stomach side in spite of the anatomical break. The same experiment was performed successfully on rabbits by Kronecker and Meltzer. Observation of the stomach end of the œsophagus in this animal showed that it went into contraction two seconds after the beginning of a swallowing act whether the œsophagus was intact or ligated or completely divided by a transverse incision. The afferent nerves concerned in this reflex are the sensory fibres to the mucous membrane of the pharynx and œsophagus, including branches of the glossopharyngeal, trigeminal, vagus, and superior laryngeal division of the vagus. Artificial stimulation of this last nerve in the lower animals is known to produce swallowing movements. Wassilieff<sup>2</sup> records that in rabbits he was able to produce the swallowing reflex by artificial stimulation of the mucous membrane of the soft palate over a definite area. The

<sup>1</sup> *Moleschott's Untersuchungen*, 1876, Bd. xi.    <sup>2</sup> *Zeitschrift für Biologie*, 1888, Bd. 24, S. 29.

sensory fibres to this area arise from the trigeminal nerve. The same observer, in experiments upon himself, was unable to locate any particular area of the mucous membrane of the mouth that seemed to be especially connected with the swallowing reflex. The physiological centre of the reflex is supposed to lie quite far forward in the medulla, but its anatomical boundaries have not been satisfactorily defined. It seems probable that in this as in other cases the physiological centre is not a circumscribed collection of nerve-cells, but comprises certain portions, more or less scattered, of the nuclei of origin of the efferent fibres to the muscles of deglutition. These muscles are innervated by fibres from the hypoglossal, facial, trigeminal, glossopharyngeal, and vagus. The latter nerve supplies through some of its branches the entire œsophagus as well as some of the pharyngeal muscles, the muscles closing the glottis, and the aryteno-epiglottidean, which is supposed to aid in depressing the epiglottis.

#### MOVEMENTS OF THE STOMACH.

The musculature of the stomach is usually divided into three layers, a longitudinal, an oblique, and a circular coat. The longitudinal coat is continuous at the cardia with the longitudinal fibres of the œsophagus; it spreads out from this point along the length of the stomach, forming a layer of varying thickness; along the curvatures the layer is stronger than on the front and posterior surfaces, while at the pyloric end it increases considerably in thickness, and passes over the pylorus to be continued directly into the longitudinal coat of the duodenum. The layer of oblique fibres is quite incomplete; it seems to be continuous with the circular fibres of the œsophagus and spreads out from the cardia for a certain distance over the front and posterior surfaces of the fundus of the stomach, but toward the pyloric end disappears, seeming to pass into the circular fibres. The circular coat, which is placed between the two preceding layers, is the thickest and most important part of the musculature of the stomach. At the extreme left end of the fundus the circular bands are thin and somewhat loosely placed, but toward the pyloric end they increase much in thickness, forming a strong muscular mass, which, as we shall see, plays the most important part in the movements of the stomach. At the pylorus itself a special development of this layer functions as a sphincter pylori, which with the aid of a circular fold of the mucous membrane makes it possible to shut off the duodenum completely or partially from the cavity of the stomach. The portion of the stomach near the pylorus is frequently designated simply as the "pyloric part," but owing to its distinct structure and functions the more specific name of "antrum pylori" seems preferable. The line of separation between the antrum pylori and the body or fundus of the stomach is made by a special thickening of the circular fibres which forms a structure known as the "transverse band" by the older writers,<sup>1</sup> and described more recently<sup>2</sup> as the "sphincter antri pylorici." This so-called sphincter lies at a distance of seven to ten centimeters from the

<sup>1</sup> See Beaumont: *Physiology of Digestion*, 2d ed., 1847, p. 104.

<sup>2</sup> Hofmeister und Schütz: *Archiv für exper. Pathologie und Pharmacologie*, 1886, Bd. xx.



pylorus. Between it and the pylorus is the "antrum pylori," of which the distinguishing features are the comparative smoothness and paleness of the mucous membrane, the presence of the pyloric as distinguished from the fundic glands, and the existence of a relatively very strong musculature.

The movements of the stomach during digestion have been the subject of much study and experimentation, both in man and the lower animals, but it cannot be said that the mechanism of the movements is as yet completely understood. The fundamental fact to be borne in mind is that during a period of several hours after ordinary food is received into the stomach the musculature of this organ contracts in such a way as to keep the contents in movement, while from time to time the thinner portions of the semi-digested food are sent through the pylorus into the duodenum. There is a certain orderliness in the movement, and especially in the separation and ejection of the more liquid from the solid parts, which indicates that the whole act is well co-ordinated to a definite end. The older physiologists spoke of a selective power of the pylorus in reference to the recurring acts of ejection of the more liquid portions into the intestine, but a phrase of this kind, as applied to a muscular apparatus, is permissible only as a figure of speech, and throws no light whatever upon the nature of the process. It has been the object of recent investigations to discover the mechanical factors involved in these acts and their relations to the musculature known to be present. It has been shown satisfactorily that the movements of the stomach are not dependent upon its connection with the central nervous system. The stomach receives a rich supply of extrinsic nerve-fibres, some of which are distributed to its muscles and serve to regulate its movements, as will be described later; but when these extrinsic nerves are all severed, and indeed when the stomach is completely removed from the body, its movements may still continue in apparently a normal way so long as proper conditions of moisture and temperature are maintained. We must believe, therefore, that the stomach is an automatic organ, using the word automatic in a limited sense to imply essential independence of the central nervous system. The normal stomach at rest is usually quiet, and the stimulus to its movements comes from the presence of the solid or liquid material received into it from the œsophagus. Upon the reception of this material the movements begin, at first feebly but gradually increasing in extent, and continue until most or all of the material has been sent into the duodenum, the length of time required depending upon the nature and amount of the food. The exact character of the movements has been variously described by different observers. Upon man they were carefully studied by Beaumont<sup>1</sup> in his famous observations upon Alexis St. Martin (see p. 288), and many points in his description have of late years been confirmed by experiments upon dogs and cats,<sup>2</sup> whose stomachs resemble that of man. These

<sup>1</sup> *The Physiology of Digestion*, 1823.

<sup>2</sup> Hofmeister und Schütz: *Archiv für exper. Pathologie und Pharmacologie*, 1886, Bd. xx.; Moritz: *Zeitschrift für Biologie*, 1895, Bd. xxxii.; Rossbach: *Deutsches Archiv für klinische Medizin*, 1890, Bd. xli.; Cannon: *American Journal of Physiology*, 1898, i. 359.

observations all tend to show that the main movements of the stomach are effected by the musculature of the antrum pylori, whose contraction is not only the chief factor in ejecting the material into the duodenum, but also aids in keeping the contents of the stomach in motion. The extent to which contractions occur in the fundic end of the stomach does not seem to be so clearly determined. According to some observers rhythmic movements are absent in the fundus to the left of about the middle of the stomach, this portion simply remaining in a condition of tone; according to others the contractions begin near the œsophageal opening and pass thence toward the pylorus. According to Cannon's observations on the cat, the fundic end toward the close of digestion enters into a gradually increasing condition of tone that squeezes its contents forward into the pre-antral region.

According to Hofmeister and Schütz, a normal movement begins near the cardia by a flattening or constriction which is feeble and is apparent only on the side of the great curvature. This constriction is due to a contraction of the circular muscle-fibres, and the wave thus started passes toward the pylorus, increasing in strength as it goes, while the parts behind previously in contraction slowly relax. This peristaltic wave comes to a stop a short distance in front of the antrum pylori by a constriction involving the whole circumference of the stomach, to which these authors gave the name of the "pre-antral" constriction; it seems to mark the climax of the peristaltic movement. The obvious effect of this movement so far would be to push forward some of the contents of the fundus into the antrum. Immediately upon the formation of this constriction the strong "sphincter antri pylorici" or transverse band which marks the beginning of the antrum, contracts strongly—so strongly, in fact, in what may be considered normal movements, as to cut off entirely the antrum pylori from the fundus. Following upon this the musculature of the antrum contracts as a whole, squeezing upon its contents and sending them through the narrow opening of the pylorus into the duodenum. If, however, the contents of the antrum are not entirely liquid, but contain some solid particles too large to escape through the narrow pylorus, their presence seems to stimulate an "antiperistaltic" wave in the musculature of the antrum pylori—that is, a muscular wave running in the reverse direction to that of a normal one, from right to left, the effect of which is to throw back these solid particles into the fundus, which is now in communication with the antrum, the sphincter antri pylorici having relaxed. This reversed wave in the antrum seems to have been observed repeatedly by Beaumont upon the human stomach, as well as by Hofmeister and Schütz upon the dog's stomach, and enables us to understand how solid particles thrown against the pylorus are again forced back into the fundus to undergo further digestive and mechanical action. According to other observers, the contractions of the sphincter antri pylorici are not strong enough to cut off completely the antrum, and the antrum does not contract as a whole. The peristaltic waves simply run over this portion with increasing strength forcing the food against the pylorus. These movements, as a whole, from fundus to pylorus occur with a certain rapidity which varies



with the nature and amount of the contents of the stomach and the period of digestion. In Beaumont's observations the movements of the pylorus are recorded as following each other at intervals of two to three minutes, while upon cats, according to Cannon's observations, the peristaltic waves in the pyloric part follow at regular intervals of about ten seconds.

It will be seen that according to this description the movements occur in two phases: first, the feeble peristaltic movement running over the fundus chiefly on the side of the great curvature and resulting in pushing some of the fundic contents into the antrum; second, the stronger contractions of the antrum, the effect of which is to squeeze some of the contents into the duodenum. Whether or not the musculature of the antrum shows only stronger peristaltic waves, or contracts as a whole, with some suddenness after the manner of a systole, as described by Hofmeister and Schütz, cannot be definitely stated. The force with which the contents of the antrum are ejected through the pylorus into the duodenum, as shown by observations made upon animals with a duodenal fistula, speaks in favor of the latter view. It is possible that either of these phases, but especially the first, might occur at times without the other, and in the first phase it is probable that the longitudinal fibres of the stomach also contract, shortening the organ in its long diameter and aiding in the propulsive movement, but actual observation of this factor has not been successfully made. It can well be understood that a series of these movements occurring at short intervals would result in putting the entire semi-liquid contents of the stomach into constant circulation. The precise direction of the current set up is not agreed upon, but it is probable that the graphic description given by Beaumont is substantially accurate. A portion of this description may be quoted, as follows: "The ordinary course and direction of the revolutions of the food are, first, after passing the œsophageal ring, from right to left, along the small arch; thence, through the large curvature, from left to right. The bolus, as it enters the cardia, turns to the left; passes the aperture; descends into the splenic extremity, and follows the great curvature toward the pyloric end. It then returns in the course of the small curvature." The average time taken for one of these complete revolutions, according to observations made by Beaumont, seems to vary from one to three minutes.

It is possible, of course, that this typical circuit taken by the food may often be varied more or less by different conditions, but the muscular movements observed from the outside would seem to be adapted to keeping up a general revolution of the kind described. The general result upon the food may easily be imagined. It becomes thoroughly mixed with the gastric juice and any liquid which may have been swallowed, and is gradually disintegrated, dissolved, and more or less completely digested so far as the proteid and albuminoid constituents are concerned. The mixing action is aided, moreover, by the movements of the diaphragm in respiration, since at each descent it presses upon the stomach. The powerful muscular contractions of the antrum serve also to triturate the softened solid particles, and finally the whole mass is reduced to a liquid or

semi-liquid mixture known as chyme, and in this condition the rhythmic contractions of the muscles of the antrum eject it into the duodenum. The rhythmic spirting of the contents of the stomach into the duodenum has been noticed by a number of observers by means of duodenal fistulas in dogs, established just beyond the pylorus. It has been shown also that when the food taken is entirely liquid—water, for example—the stomach is emptied in a surprisingly short time, within twenty to thirty minutes; if, however, the water is taken with solid food then naturally the time it will remain in the stomach may be much lengthened.

A very interesting part of the mechanism of the stomach the action of which is not thoroughly understood is the sphincter of the pylorus. During the act of digestion this sphincter remains in a condition of tone; whether its tonic contraction is sufficient only to narrow the pylorus, or whether it is sufficient to completely shut off the pylorus so that a partial relaxation must occur with each contraction of the musculature of the antrum, is not sufficiently well known. It has been shown, however, that this part of the circular layer of muscle is distinctly under the control of the extrinsic nerves, its tonicity being increased by impulses received through the vagi and diminished or inhibited by impulses through the splanchnics. It will be seen from the above brief description that the muscles of the antrum pylori do most of the work of the stomach, while in the much larger fundus the food is retained as in a reservoir to be digested and mechanically prepared for expulsion into the intestine, the two parts of the stomach fulfilling therefore somewhat different functions. Moritz<sup>1</sup> has called especial attention to this fact, and points out the great advantage which accrues to the digestive processes in the intestine in having the stomach to retain the bulk of the food swallowed during a meal, while from time to time small portions only are sent into the intestine for more complete digestion and absorption. In this way the intestine is protected from becoming congested, and its digestive and absorptive processes are more perfectly executed.

**Extrinsic Nerves to the Muscles of the Stomach.**—The musculature of the stomach receives extrinsic nerve-fibres from two sources: from the two vagi and from the solar plexus. The fibres from the latter source arise ultimately in the spinal cord, pass to some of the thoracic ganglia of the sympathetic system, and thence by way of the splanchnics to the semilunar or solar plexus and then to the stomach. These fibres probably reach the stomach as non-medullated or sympathetic fibres. The vagi where they are distributed to the stomach seem to consist almost entirely of non-medullated fibres also, and probably the fibres distributed to the muscular coat are of this variety. The results of numerous experiments seem to show quite conclusively that in general the fibres received along the vagus path are motor, artificial stimulation of them causing more or less well marked contractions of part or all of the musculature of the stomach. It has been shown that the sphincter pylori as well as the rest of the musculature is supplied by motor fibres from these

<sup>1</sup> *Zeitschrift für Biologie*, 1895, Bd. xxiii.



nerves. The fibres coming through the splanchnics, on the contrary, are mainly inhibitory. When stimulated they cause a dilatation of the contracted stomach and a relaxation of the sphincter pylori. Some observers have reported experiments which seem to show that this anatomical separation of the motor and inhibitory fibres is not complete; that some inhibitory fibres may be found in the vagi and some motor fibres in the splanchnics. The anatomical courses of these fibres are insufficiently known, but there seems to be no question as to the existence of the two physiological varieties. Through their activity, without doubt, the movements of the stomach may be regulated, favorably or unfavorably, by conditions directly or indirectly affecting the central nervous system. Wertheimer<sup>1</sup> has shown experimentally that stimulation of the central end of the sciatic or the vagus nerve may cause reflex inhibition of the tonus of the stomach, and Doyon<sup>2</sup> has confirmed this result in cases where the movements and tonicity of the stomach were first increased by the action of pilocarpin and strychnin. Cannon in his observations upon cats found that all movements of the stomach ceased as soon as the animal showed signs of anxiety, rage, or distress. It must be borne in mind, however, that the action of these extrinsic fibres under normal conditions is probably only to regulate the movements of the stomach. As we have seen, even the extirpated stomach under proper conditions seems to execute movements of the normal type. Normally the movements are provoked by a stimulus of some kind, usually the presence of food material in the interior of the stomach. How the stimulus acts in this case, whether directly upon the muscle-fibres or indirectly through the intrinsic ganglia of the stomach, has not been determined, and the evidence for either view is so insufficient that a discussion of the matter at this time would scarcely be profitable. We must wait for more complete investigations upon the physiology as well as the histology of the muscle- and nerve-tissue in this and in other visceral organs constructed on the same type.

#### MOVEMENTS OF THE INTESTINES.

The muscles of the small and the large intestine are arranged in two layers, an outer longitudinal and an inner circular coat, while between these coats and in the submucous coat there are present the nerve-plexuses of Auerbach and Meissner. The general arrangement of muscles and nerves is similar, therefore, to that prevailing in the stomach, and in accordance with this we find that the physiological activities exhibited are of much the same character, only, perhaps, not quite so complex.

**Forms of Movement.**—Two main forms of intestinal movement have been distinguished, the peristaltic and the pendular.

**Peristalsis.**—The peristaltic movement consists in a constriction of the walls of the intestine which beginning at a certain point passes downward away from the stomach, from segment to segment, while the parts behind the advancing zone of constriction gradually relax. The evident effect of such a movement

<sup>1</sup> *Archives de Physiologie normale et pathologique*, 1892, p. 379.

<sup>2</sup> *Ibid.*, 1895, p. 374.

would be to push onward the contents of the intestines in the direction of the movement. It is obvious that the circular layer of muscles is chiefly involved in peristalsis, since constriction can only be produced by contraction of this layer. To what extent the longitudinal muscles enter into the movement is not definitely determined. The term "anti-peristalsis" is used to describe the same form of movement running in the opposite direction—that is, toward the stomach. Anti-peristalsis is usually said not to occur under normal conditions; it has been observed sometimes in isolated pieces of intestine or in the exposed intestine of living animals when stimulated artificially, and Grützner<sup>1</sup> reports a number of curious experiments which seem to show that substances such as hairs, animal charcoal, etc., introduced into the rectum may travel upward to the stomach under certain conditions. The peristaltic wave normally passes downward, and that this direction of movement is dependent upon some definite arrangement in the intestinal walls is beautifully shown by the experiments of Mall<sup>2</sup> and others upon reversal of the intestines. In these experiments a portion of the small intestine was resected, turned round and sutured in place again, so that in this piece what was the lower end became the upper end. In those animals that made a good operative recovery the nutritive condition gradually became very serious, and in the animals killed and examined the autopsy showed accumulation of material at the upper end of the reversed piece of intestine, and great dilatation.

The peristaltic movements of the intestines may be observed upon living animals when the abdomen is opened. If the operation is made in the air and the intestines are exposed to its influence, or if the conditions of temperature and circulation are otherwise disturbed, the movements observed are often violent and irregular. The peristalsis runs rapidly along the intestines and may pass over the whole length in about a minute; at the same time the contraction of the longitudinal muscles gives the bowels a peculiar writhing movement. Movements of this kind are evidently abnormal, and only occur in the body under the strong stimulation of pathological conditions. Normal peristalsis, the object of which is to move the food slowly along the alimentary tract, is quite a different affair. Observers all agree that the wave of contraction is gentle and progresses slowly. According to Bayliss and Starling,<sup>3</sup> the peristaltic movement is a complicated reflex through the intrinsic ganglia. When the intestine is stimulated by a bolus placed within its cavity, the musculature above the point stimulated is excited, while that below is inhibited. In accordance with this law they find that in peristalsis the advancing wave of constriction is preceded by a wave of relaxation or inhibition. The force of the contraction as measured by Cash<sup>4</sup> in the dog's intestine is very small. A weight of five to eight grams was sufficient to check the onward movement of the substance in the intestine and to set up violent colicky

<sup>1</sup> *Deutsche medicinische Wochenschrift*, 1894, No. 48.

<sup>2</sup> *The Johns Hopkins Hospital Reports*, vol. i p. 93.

<sup>3</sup> *Journal of Physiology*, 1899, vol. xxiv p. 99.

<sup>4</sup> *Proceedings of the Royal Society, London*, 1887, vol. 41.



contractions which caused the animal evident uneasiness. We may suppose that under normal conditions each contraction of the antrum pylori of the stomach, which ejects chyme into the duodenum, is followed by a peristalsis that beginning at the duodenum passes slowly downward for a part or all of the small intestine. According to most observers, the movement is blocked at the ileo-cæcal valve, and the peristaltic movements of the large intestine form an independent group similar in all their general characters to those of the small intestine, but weaker and slower.

*Mechanism of the Peristaltic Movement.*—The means by which the peristaltic movement makes its orderly forward progression have not been determined beyond question. The simplest explanation would be to assume that an impulse is conveyed directly from cell to cell in the circular muscular coat, so that a contraction started at any point would spread by direct conduction of the contraction change. This theory, however, does not explain satisfactorily the normal conduction of the wave of contraction always in one direction, nor the fact that a reversed piece of intestine continues to send its waves in what was for it the normal direction. Moreover, Bayliss and Starling state that although the peristaltic movements continue after section of the extrinsic nerves—indeed, become more marked under these conditions—the application of cocaine or nicotine prevents their occurrence. Since these substances may be supposed to act on the intrinsic nerves, it is probable that the co-ordination of the movement is effected through the local nerve-ganglia, but our knowledge of the mechanism and physiology of these peripheral nerve-plexuses is as yet quite incomplete.

*Pendular Movements.*—In addition to the peristaltic wave a second kind of movement may be observed in the exposed intestines of a living animal. This movement is characterized by a gentle swinging to and fro of the different loops, whence its name of pendular movement. The oscillations occur at regular intervals, and are usually ascribed to rhythmic contractions of the longitudinal muscles. Mall,<sup>1</sup> however, believes that the main feature of this movement is a rhythmic contraction of the circular muscles, involving a part or all of the intestines. He prefers to speak of the movements as rhythmic instead of pendular contractions, and points out that owing to the arrangement of the blood-vessels in the coats of the intestine the rhythmic contractions should act as a pump to expel the blood from the submucous venous plexus into the radicles of the superior mesenteric vein, and thus materially aid in keeping up the circulation through the intestine and in maintaining a good pressure in the portal vein, in much the same way as happens in the case of the spleen (see p. 332). Bayliss and Starling corroborate this view, except that they find that both the circular and longitudinal layers of muscle are concerned in the movement. The rhythmic contractions, according to these observers, are entirely muscular in origin, since they persist after the application of nicotine or cocaine.

*Extrinsic Nerves of the Intestines.*—As in the case of the stomach, the

<sup>1</sup> *The Johns Hopkins Hospital Reports*, vol. i. p. 37.

small intestine and the greater part of the large intestine receive viscero-motor nerve-fibres from the vagi and the sympathetic chain. The former, according to most observers, when artificially stimulated cause movements of the intestine, and are therefore regarded as the motor fibres. It seems probable, however, that the vagi carry or may carry in some animals inhibitory fibres as well, and that the motor effects usually obtained upon stimulation are due to the fact that in these nerves the motor fibres predominate. The fibres received from the sympathetic chain, on the other hand, give mainly an inhibitory effect when stimulated, although some motor fibres apparently may take this path. Beecherew and Mislawski<sup>1</sup> state that the sympathetic fibres for the small intestine emerge from the spinal cord as medullated fibres in the sixth dorsal to the first lumbar spinal nerves, and pass to the sympathetic chain in the splanchnic nerves and thence to the semilunar plexus, while the sympathetic fibres to the large intestine and rectum arise in the four lower lumbar and the three upper sacral spinal nerves. According to Langley and Anderson<sup>2</sup> the descending colon and rectum receive a double nerve-supply—first from the lumbar spinal nerves (second to fifth), the fibres passing through the sympathetic ganglia and the inferior mesenteric plexus and causing chiefly an inhibition; second, through the sacral nerves, the fibres passing through the nervus erigens and the hypogastric plexus and causing chiefly contraction of the circular muscle.

These extrinsic fibres undoubtedly serve for the regulation of the movements of the bowels from the central nervous system; conditions which influence the central system, either directly or indirectly, may thus affect the intestinal movements. The paths of these fibres through the central nervous system are not known, but there are evidently connections extending to the higher brain-centres, since psychical states are known to influence the movements of the intestine, and according to some observers stimulation of portions of the cerebral cortex may produce movements or relaxation of the walls of the small and large intestines. As in the case of the stomach, the extrinsic fibres seem to have only a regulatory influence. When they are completely severed the tonicity of the walls of the intestine is not altered, and peristaltic and rhythmic movements still occur. The same results may be obtained even upon excised portions of the intestines (Salvioli, Mall). It seems probable, therefore, that normal peristalsis in the living animal may be effected independently of the central nervous system, although its character and strength is subject to regulation through the medium of the viscero-motor fibres, in much the same way, and possibly to as great an extent, as the movements of the heart are controlled through its extrinsic nerves.

**Effect of Various Conditions upon the Intestinal Movements.**—Experiments have shown that the movements of the intestines may be evoked in many ways beside direct stimulation of the extrinsic nerves. Chemical stimuli may be applied directly to the intestinal wall. Mechanical stimulation, pinching, for example, or the introduction of a bolus into the intestinal cavity, will

<sup>1</sup> Du Bois-Reymond's *Archiv für Physiologie*, 1889, Suppl. Bd.

<sup>2</sup> *Journal of Physiology*, 1895, vol. xviii, p. 67.



start normal peristalsis. Violent movements may be produced also by shutting off the blood-supply, and again temporarily when the supply is re-established. A condition of dyspnoea may also start movements in the intestines or in some cases inhibit movements which are already in progress, the stimulus in this case seeming to act upon the central nervous system and to stimulate both the motor and the inhibitory fibres. Oxygen gas within the bowels tends to suspend the movements of the intestine, while  $\text{CO}_2$ ,  $\text{CH}_4$ , and  $\text{H}_2\text{S}$  act as stimuli, increasing the movements. Organic acids, such as acetic, propionic, formic, and caprylic, which may be formed normally within the intestine as the result of bacterial action, act also as strong stimulants.<sup>1</sup>

**Defecation.**—The undigested and indigestible parts of the food, together with some of the debris and secretions from the alimentary tract, are carried slowly through the large intestine by its peristaltic movements and eventually reach the sigmoid flexure and rectum. Here the nearly solid material stimulates by its pressure the sensory nerves of the rectum and produces a distinct sensation and desire to defecate. The fecal material is retained within the rectum by the action of the two sphincter muscles which close the anal opening. One of these muscles, the internal sphincter, is a strong band of the circular layer of involuntary muscles which forms one of the coats of the rectum. When the rectum contains fecal material this muscle seems to be thrown into a condition of tonic contraction until the act of defecation begins, when it is relaxed. The sphincter is composed of involuntary muscle and is innervated by fibres arising partly from the sympathetic system, and in part through the nervus erigens, from the sacral spinal nerves. The external sphincter ani is composed of striated muscle-tissue and is under the control of the will to a certain extent. When, however, the stimulus from the rectum is sufficiently intense, voluntary control is overcome and this sphincter is also relaxed. The act of defecation is in part voluntary and in part involuntary. The involuntary factor is found in the contractions of the strongly developed musculature of the rectum, especially the circular layer, which serves to force the feces onward, and the relaxation of the internal sphincter. It seems that these two acts are mainly caused by reflex stimulation from the lumbar spinal cord, although it is probable that the rectum, like the rest of the alimentary tract, is capable of automatic contractions. The rectal muscles receive a double nervous supply, containing physiologically both motor and inhibitory fibres. Some of these fibres come from the nervus erigens by way of the hypogastric plexus, and some arise from the lumbar cord and pass through the corresponding sympathetic ganglia, inferior mesenteric ganglion, and hypogastric nerve. It has been asserted that stimulation of the nervus erigens causes contraction of the longitudinal muscles and inhibition of the circular muscles, while stimulation of the hypogastric nerve causes contraction of the circular muscles and inhibition of the longitudinal layer. This division of activity is not confirmed by the recent experiments of Langley and Anderson.<sup>2</sup>

The voluntary factor in defecation consists in the inhibition of the external

<sup>1</sup> Bokai: *Archiv für exper. Pathologie und Pharmacologie*, 1888, Bd. 24, S. 153.

<sup>2</sup> *Op. cit.*

sphincter and the contraction of the abdominal muscles. When these latter muscles are contracted and at the same time the diaphragm is prevented from moving upward by the closure of the glottis, the increased abdominal pressure is brought to bear upon the abdominal and pelvic viscera, and aids strongly in pressing the contents of the descending colon and sigmoid flexure into the rectum. The pressure in the abdominal cavity is still further increased if a deep inspiration is first made and then maintained during the contraction of the abdominal muscles. Although the act of defecation is normally initiated by voluntary effort, it may also be aroused by a purely involuntary reflex when the sensory stimulus is sufficiently strong. Goltz<sup>1</sup> has shown that in dogs in which the spinal cord had been severed in the lower thoracic region defecation was performed normally. In later experiments in which the entire spinal cord was removed, except in the cervical and upper part of the thoracic region, it was found that the animal after it had recovered from the operation had normal movement once or twice a day, indicating that the rectum and lower bowels acted by virtue of their intrinsic mechanism. A curious result of these experiments was the fact that the external sphincter eventually regained its tonic activity.

It would seem that the whole act of defecation is at bottom an involuntary reflex. The physiological centre for the movement probably lies in the lumbar cord, and has sensory and motor connections with the rectum and the muscles of defecation, but this centre is in part at least provided with connections with the centres of the cerebrum through which the act may be controlled by voluntary impulses and by various psychical states, the effect of emotions upon defecation being a matter of common knowledge. In infants the essentially involuntary character of the act is well seen.

**Vomiting.**—The act of vomiting causes an ejection of the contents of the stomach through the œsophagus and mouth to the exterior. It was long debated whether the force producing this ejection comes from a strong contraction of the walls of the stomach itself or whether it is due mainly to the action of the walls of the abdomen. A forcible spasmodic contraction of the abdominal muscles takes place, as may easily be observed by any one upon himself, and it is now believed that the contraction of these muscles is the principal factor in vomiting. Magendie found that if the stomach was extirpated and a bladder containing water was substituted in its place and connected with the œsophagus, injection of an emetic caused a typical vomiting movement with ejection of the contents of the bladder. Gianuzzi showed, on the other hand, that upon a curarized animal vomiting could not be produced by an emetic—because, apparently, the muscles of the abdomen were paralyzed by the curare. There are on record, however, a number of observations which tend to show that the stomach is not entirely passive during the act. On the contrary, it may exhibit contractions, more or less violent in character, which while insufficient in themselves to eject its contents, probably aid in a normal act of vomiting. According to Openchowski,<sup>2</sup> the pylorus is closed and the pyloric end of the

<sup>1</sup> *Archiv für die gesammte Physiologie*, 1874, Bd. viii. S. 460; also Bd. lxiii. S. 362.

<sup>2</sup> *Archiv für Physiologie*, 1889, S. 552.



stomach firmly contracted so as to drive the contents toward the dilated cardiac portion. The act of vomiting is in fact a complex reflex movement into which many muscles enter. The following events are described: The vomiting is usually preceded by a sensation of nausea and a reflex flow of saliva into the mouth. These phenomena are succeeded or accompanied by retching movements, which consist essentially in deep spasmodic inspirations with a closed glottis. The effect of these movements is to compress the stomach by the descent of the diaphragm, and at the same time to increase decidedly the negative pressure in the thorax, and therefore in the thoracic portion of the œsophagus. During one of these retching movements the act of vomiting is effected by a convulsive contraction of the abdominal wall that exerts a sudden additional strong pressure upon the stomach. At the same time the cardiac orifice of the stomach is dilated, possibly by an inhibition of the sphincter, aided it is supposed by the contraction of the longitudinal muscle-fibres of the œsophagus and the oblique fibres of the muscular coat of the stomach. The stomach contents are, therefore, forced violently out of the stomach through the œsophagus, the negative pressure in the latter probably assisting in the act. The passage through the œsophagus is effected mainly by the force of the contraction of the abdominal muscles; there is no evidence of antiperistaltic movements on the part of the œsophagus itself. During the ejection of the contents of the stomach the glottis is kept closed by the adductor muscles, and usually the nasal chamber is likewise shut off from the pharynx by the contraction of the posterior pillars of the fauces on the palate and uvula. In violent vomiting, however, the vomited material may break through this latter barrier and be ejected partially through the nose.

*Nervous Mechanism of Vomiting.*—That vomiting is a reflex act is abundantly shown by the frequency with which it is produced in consequence of the stimulation of sensory nerves or as the result of injuries to various parts of the central nervous system. After lesions or injuries of the brain vomiting often results. Disagreeable emotions and disturbances of the sense of equilibrium may produce the same result. Irritation of the mucous membrane of various parts of the alimentary canal (as, for example, tickling the back of the pharynx with the finger), disturbances of the urogenital apparatus, artificial stimulation of the trunk of the vagus and of other sensory nerves, may all cause vomiting. Under ordinary conditions, however, irritation of the sensory nerves of the gastric mucous membrane is the most common cause of vomiting. This effect may result from the products of fermentation in the stomach in cases of indigestion, or may be produced intentionally by local emetics, such as mustard, taken into the stomach. The afferent path in this case is through the sensory fibres of the vagus. The efferent paths of the reflex are found in the motor nerves innervating the muscles concerned in the vomiting, namely, the vagus, the phrenics, and the spinal nerves supplying the abdominal muscles. Whether or not there is a definite vomiting centre in which the afferent impulses are received and through which

a co-ordinated series of efferent impulses is sent out to the various muscles, has not been satisfactorily determined. It has been shown that the portion of the nervous system through which the reflex is effected lies in the medulla. But it has been pointed out that the muscles concerned in the act are respiratory muscles. Vomiting in fact consists essentially in a simultaneous spasmodic contraction of expiratory (abdominal) muscles and inspiratory muscles (diaphragm). It has therefore been suggested that the reflex takes place through the respiratory centre, or some part of it. This view seems to be opposed by the experiments of Thumas,<sup>1</sup> who has shown that when the medulla is divided down the mid-line respiratory movements continue as usual, but vomiting can no longer be produced by the use of emetics. Thumas claims to have located a vomiting centre in the medulla in the immediate neighborhood of the calamus scriptorius. Further evidence, however, is required upon this point. The act of vomiting may be produced not only as a reflex from various sensory nerves, but may also be caused by direct action upon the medullary centres. The action of apomorphia is most easily explained by supposing that it acts directly on the nerve-centres.

**Micturition.**—The urine is secreted continuously by the kidneys, is carried to the bladder through the ureters, and is then at intervals finally ejected from the bladder through the urethra by the act of micturition.

**Movements of the Ureters.**—The ureters possess a muscular coat consisting of an internal longitudinal and external circular layer. The contractions of this muscular coat are the means by which the urine is driven from the pelvis of the kidney into the bladder. The movements of the ureter have been carefully studied by Engelmann.<sup>2</sup> According to his description the musculature of the ureter contracts spontaneously at intervals of ten to twenty seconds (rabbit), the contraction beginning at the kidney and progressing toward the bladder in the form of a peristaltic wave and with a velocity of about twenty to thirty millimeters per second. The result of this movement should be the forcing of the urine into the bladder in a series of gentle rhythmic spurts, and this method of filling the bladder has been observed in the human being. Suter and Mayer<sup>3</sup> report some observations upon a boy in whom there was ectopia of the bladder with exposure of the orifices of the ureters. The flow into the bladder was intermittent and was about equal upon the two sides for the time the child was under observation (three and a half days).

The causation of the contractions of the ureter musculature is not easily explained. Engelmann finds that artificial stimulation of the ureter or of a piece of the ureter may start peristaltic contractions which move in both directions from the point stimulated. He was not able to find ganglion-cells in the upper two-thirds of the ureter, and was led to believe, therefore, that the contraction originates in the muscular tissue independently of extrinsic or intrinsic nerves, and that the contraction wave propagates itself directly from muscle-

<sup>1</sup> *Virchow's Archiv für pathologische Anatomie*, etc., 1891, Bd. 123, S. 44.

<sup>2</sup> *Pflüger's Archiv für die gesammte Physiologie*, 1869, Bd. ii. S. 243; Bd. iv. S. 33.

<sup>3</sup> *Archiv für exper. Pathologie und Pharmacologie*, 1893, Bd. 32, S. 241.



cell to muscle-cell, the entire musculature behaving as though it were a single, colossal hollow muscle-fibre. The liberation of the stimulus which inaugurates the normal peristalsis of the ureter seems to be connected with the accumulation of urine in its upper or kidney portion. It may be supposed that the urine that collects at this point as it flows from the kidney stimulates the muscular tissue to contraction, either by its pressure or in some other way, and thus leads to an orderly sequence of contraction waves. It is possible, however, that the muscle of the ureter, like that of the heart, is spontaneously contractile under normal conditions, and does not depend upon the stimulation of the urine. Thus, according to Engelmann, section of the ureter near the kidney does not materially affect the nature of the contractions of the stump attached to the kidney, although in this case the pressure of the urine could scarcely act as a stimulus. Moreover, in the case of the rat, in which the ureter is highly contractile, the tube may be cut into several pieces and each piece will continue to exhibit periodic peristaltic contractions. It does not seem possible at present to decide between these two views as to the cause of the contractions. The nature of the contractions, their mode of progression, and the way in which they force the urine through the ureter seem, however, to be clearly established. Efforts to show a regulatory action upon these movements through the central nervous system have so far given only negative results.

*Movements of the Bladder.*—The bladder contains a muscular coat of plain muscle-tissue, which, according to the usual description, is arranged so as to make an external longitudinal coat and an internal circular or oblique coat. A thin longitudinal layer of muscle-tissue lying to the interior of the circular coat is also described. The separation between the longitudinal and circular layers is not so definite as in the case of the intestine; they seem, in fact, to form a continuous layer, one passing gradually into the other by a change in the direction of the fibres. At the cervix the circular layer is strengthened, and has been supposed to act as a sphincter with regard to the urethral orifice—the so-called sphincter vesicæ internus. Round the urethra just outside the bladder is a circular layer of striated muscle that is frequently designated as the external sphincter or sphincter urethræ. The urine brought into the bladder accumulates within its cavity to a certain limit. It is prevented from escaping through the urethra at first by the mere elasticity of the parts at the urethral orifice, aided perhaps by tonic contraction of the internal sphincter, although this function of the circular layer is disputed by some observers. When the accumulation becomes greater the external sphincter is brought into action. If the desire to urinate is strong the external sphincter seems undoubtedly to be controlled by voluntary effort, but whether or not, in moderate filling of the bladder, it is brought into play by an involuntary reflex is not definitely determined. Back-flow of urine from the bladder into the ureters is effectually prevented by the oblique course of the ureters through the wall of the bladder. Owing to this circumstance pressure within the bladder serves to close the mouths of the ureters, and indeed the more completely the higher the pressure. At some point in the filling of the bladder the pressure is sufficient to

arouse a conscious sensation of fulness and a desire to micturate. Under normal conditions the act of micturition follows. It consists essentially in a strong contraction of the bladder with a simultaneous relaxation of the external sphincter, if this muscle is in action, the effect of which is to obliterate more or less completely the cavity of the bladder and drive the urine out through the urethra.

The force of this contraction is considerable, as is evidenced by the height to which the urine may spirt from the end of the urethra. According to Mosso the contraction may support, in the dog, a column of liquid two meters high. The contractions of the bladder may be and usually are assisted by contractions of the walls of the abdomen, especially toward the end of the act. As in defecation and vomiting, the contraction of the abdominal muscles, when the glottis is closed so as to keep the diaphragm fixed, serves to increase the pressure in the abdominal and pelvic cavities, and is thus used to assist in or complete the emptying of the bladder. It is, however, not an essential part of the act of micturition. The last portions of the urine escaping into the urethra are ejected, in the male, in spurts produced by the rhythmic contractions of the bulbo-cavernosus muscle.

Considerable uncertainty and difference of opinion exists as to the physiological mechanism by which this series of muscular contractions, and especially the contractions of the bladder itself, is produced. According to the frequently quoted description given by Goltz<sup>1</sup> the series of events is as follows: The distention of the bladder by the urine causes finally a stimulation of the sensory fibres of the organ and produces a reflex contraction of the bladder musculature which squeezes some urine into the urethra. The first drops, however, that enter the urethra stimulate the sensory nerves there and give rise to a conscious desire to urinate. If no obstacle is presented the bladder then empties itself, assisted perhaps by the contractions of the abdominal muscles. The emptying of the bladder may, however, be prevented, if desirable, by a voluntary contraction of the sphincter urethræ, which opposes the effect of the contraction of the bladder. If the bladder is not too full and the sphincter is kept in action for some time, the contractions of the bladder may cease and the desire to micturate pass off. According to this view the voluntary control of the process is limited to the action of the external sphincter and the abdominal muscles; the contraction of the bladder itself is purely an unconscious reflex taking place through a lumbar centre.

The experiments of Goltz and others, upon dogs in which the spinal cord was severed at the junction of the lumbar and the thoracic regions, indicate that micturition is essentially a reflex act with its centre in the lumbar cord, although the same observer has shown that in dogs whose spinal cord has been entirely destroyed, except in the cervical and upper thoracic region, the bladder empties itself normally without the aid of external stimulation. Mosso and Pellacani<sup>2</sup> have made experiments upon women which seem to

<sup>1</sup> *Archiv für die gesamte Physiologie*, 1874, Bd. viii. S. 478.

<sup>2</sup> *Archives italiennes de Biologie*, 1882, tome i.



show that the bladder may be emptied by a direct voluntary act. In these experiments a catheter was introduced into the bladder and connected with a recording apparatus to measure the volume of the bladder. It was found that, in some cases at least, the woman could empty the bladder at will without using the abdominal muscles. The same authors adduce experimental evidence to show that the sensation of fulness and desire to micturate come from sensory stimulation in the bladder itself caused by the pressure of the urine. They point out that the bladder is very sensitive to reflex stimulation; that every psychical act and every sensory stimulus is apt to cause a contraction or increased tone of the bladder. The bladder is, therefore, subject to continual changes in size from reflex stimulation, and the pressure within it will depend not simply on the quantity of urine, but on the condition of tone of the bladder. At a certain pressure the sensory nerves are stimulated and under normal conditions micturition ensues. We may understand, from this point of view, how it happens that we have sometimes a strong desire to micturate when the bladder contains but little urine—for example, under emotional excitement. In such cases if the micturition is prevented, probably by the action of the external sphincter, the bladder may subsequently relax and the sensation of fulness and desire to micturate pass away until the urine accumulates in sufficient quantity or the pressure is again raised by some circumstance which causes a reflex contraction of the bladder.

*Nervous Mechanism.*—According to a recent paper by Langley and Anderson,<sup>1</sup> the bladder in cats, dogs, and rabbits receives motor fibres from two sources: (1) From the lumbar nerves, the fibres passing out in the second to the fifth lumbar nerves and reaching the bladder through the sympathetic chain and the inferior mesenteric ganglion and hypogastric nerves. Stimulation of these nerves causes comparatively feeble contraction of the bladder. (2) From the sacral spinal nerves, the fibres originating in the second and third sacral spinal nerves, or in the rabbit in the third and fourth, and being contained in the so-called *nervus erigens*. Stimulation of these nerves, or some of them, causes strong contractions of the bladder, sufficient to empty its contents. Little evidence was obtained of the presence of vaso-motor fibres. According to Nawrocki and Skabitschewsky<sup>2</sup> the spinal sensory fibres to the bladder are found in part in the posterior roots of the first, second, third, and fourth sacral spinal nerves, particularly the second and third. When these fibres are stimulated they excite reflexly the motor fibres to the bladder found in the anterior roots of the second and third sacral spinal nerves. Some sensory fibres to the bladder pass by way of the hypogastric nerves. When these are stimulated they produce, according to these authors, a reflex effect upon the motor fibres in the other hypogastric nerve, causing a contraction of the bladder, the reflex occurring through the inferior mesenteric ganglion. This observation has been confirmed by several authorities, and is the best example of a peripheral ganglion serving as a reflex

<sup>1</sup> *Journal of Physiology*, 1895, vol. xix, p. 71.

<sup>2</sup> *Archiv für die gesammte Physiologie*, 1891, Bd. 49, S. 141.

centre. Langley and Anderson,<sup>1</sup> who also obtained this effect, give it a special explanation, contending that it is not a true reflex.

The immediate spinal centre through which the contractions of the bladder may be reflexly stimulated or inhibited lies, according to the experiments of Goltz, in the lumbar portion of the cord, probably between the second and fifth lumbar spinal nerves. In dogs in which this portion of the cord was isolated by a cross section at the junction of the thoracic and lumbar regions, micturition still ensued when the bladder was sufficiently full, and could be called forth reflexly by sensory stimuli, especially by slight irritation of the anal region. This localization has been confirmed by others.<sup>2</sup>

*Movements of other Visceral Organs.*—For the characteristics of the movements of other viscera reference must be made to the appropriate sections. The movements of the arteries are described under Circulation, those of the uterus under Reproduction.

<sup>1</sup> *Journal of Physiology*, 1894, vol. xvi. p. 410; see also Justschenko: *Archives des Sciences biologiques*, 1898, t. 6, p. 536.

<sup>2</sup> See Stewart: *American Journal of Physiology*, 1899, vol. ii. p. 182.





## VII. RESPIRATION.

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A STUDY of the phenomena of animal life teaches us that a supply of oxygen and an elimination of carbon dioxide are essential to existence. Oxygen is indispensable to life; carbon dioxide is inimical to life. One serves for the disintegration of complex molecules whereby energy is evolved, while the other is one of the main effete products of this dissociation. We therefore find an intimate relationship between the ingress of the one and the egress of the other. During the entire life of the individual there is this continual interchange, which we term *respiration*. This term embraces two acts which, while different, are nevertheless co-operative—first, the interchange of O and CO<sub>2</sub>; second, the movements of certain parts of the body, having for their object the inflow and outflow of air to and from the lungs. The former, properly speaking, is *respiration*; the latter, *movements of respiration*.

Respiration is spoken of as *internal* and as *external* respiration. In the very lowest forms of life the interchange of gases takes place directly between the various parts of the organism and the air or the water in which the organism lives; but in higher beings a circulating fluid becomes a means of exchange between the bodily structures and the surrounding medium, so that in these beings there is first an interchange between the air or the water in which the animal lives and the circulating medium, and subsequently an interchange between the circulating medium and the tissues. Therefore in the most primitive forms of life respiration is a single process, while in higher organisms it is a dual process, or one consisting of two stages, the first being the interchange between the atmosphere or the water surrounding the body and the circulating medium, and the second between the circulating medium and the bodily structures. In man, external respiration is the interchange taking place between the blood and the gases in the lungs and, to a very small extent, between the blood and the air through the skin; while internal respiration is the interchange between the blood and the tissues. In external respiration O is absorbed and CO<sub>2</sub> is given off by the blood; in internal respiration the blood absorbs CO<sub>2</sub> and gives off O.

### A. THE RESPIRATORY MECHANISM IN MAN.

The respiratory apparatus in man consists (1) of the lungs and the air-passages leading to them, the thorax and the muscular mechanisms by means of which the lungs are inflated and emptied, and the nervous mechanisms connected therewith; and (2) the skin, which, however, plays a subsidiary part in man, and need not here be considered.



The lungs may be regarded as two large bags broken up into saccular divisions and subdivisions which ultimately consist of a vast number of little pouches, or infundibuli, each of which is, as the name implies, funnel-shaped, the walls being hollowed out into alveoli, or air-vesicles. These alveoli vary in size from  $120\mu$  to  $380\mu$ , the average diameter being about  $250\mu$  ( $\frac{1}{100}$  inch). Each infundibulum communicates by means of a small air-passage with a bronchiole, which in turn communicates with a smaller air-tube or bronchus, and finally, through successive unions, with the common air-duct or trachea. It is estimated that the alveoli number about 725,000,000, and that the total superficies exposed by them to the gases in the lungs is about 200 square meters, or from one hundred to one hundred and thirty times greater than the surface of the body (1.5 to 2 square meters). The wall of each alveolus forms a delicate partition between the air in the lungs and an intricate network of blood-vessels; this network is so dense that the spaces between the capillaries are, as a rule, smaller than the diameters of the vessels. The lungs, therefore, are exceedingly vascular, and it is estimated that the vessels contain on an average about 1.5 kilograms of blood. Owing to the minuteness of the capillaries and the density of the network, the air-cells may be said to be surrounded by a film of blood which is about  $10\mu$  in thickness and has an area of about 150 square meters.

The lungs are highly elastic, and their elasticity is perfect, as is shown by the fact that they immediately regain their passive condition as soon as the dilating or distending force has been removed. Before birth the lungs are airless (*atelectatic*) and the walls of the bronchioles and the infundibuli are in contact, yet in the child before birth, as in the adult, the lungs are in apposition with the thoracic walls, being separated only by two layers of the pleuræ. As soon as the child is born a few respiratory movements are sufficient to inflate them, and thereafter they never regain their atelectatic condition, since after the most complete collapse, such as occurs when the thorax is opened, some air remains in the alveoli, owing to the fact that the walls of the bronchioles come together before all of the air can escape. As the child grows the thorax increases in size more rapidly than the lungs, and becomes too large, as it were, for the lungs, which, as a consequence, become permanently distended because of their being in an air-tight cavity. If the chest of a cadaver be punctured, the lungs immediately shrink so that a considerable air-space will be formed between them and the walls of the thorax. This collapse is due to the condition of elastic tension which exists from the moment air is introduced into the alveoli, and which increases with the degree of expansion. Therefore, after the lungs are inflated they exhibit a persistent tendency to collapse; consequently they must exercise upon the thoracic walls and diaphragm a constant traction or "pull" which is in proportion to the amount of tension. It is therefore obvious that there must exist within the thorax, under ordinary circumstances, a state of *negative* pressure (pressure below that of the atmosphere). This can be proven by connecting a trocar with a manometer and then forcing the trocar into one of the pleural sacs.

Donders found that the pressure at the end of quiet expiration was  $-6$  millimeters of Hg, and at the end of quiet inspiration  $-9$  millimeters. According to these figures, the pressure on the heart, great blood-vessels, and other thoracic structures lying between the lungs and the thoracic walls would be 754 millimeters of Hg (one atmosphere, 760 millimeters,  $-6$  millimeters) at the end of quiet expiration, and 751 millimeters of Hg at the end of quiet inspiration. Corresponding values by Hutchinson are  $-3$  millimeters and  $-4.5$  millimeters. Arron<sup>1</sup> found in a case of a woman with emphysema that the pressure at the end of expiration ranged from  $-1.9$  to  $-3.9$  millimeters, and at the end of inspiration from  $-4$  to  $-6.85$  millimeters, according to the position of the body, the pressure being lowest in the lying posture, higher when sitting in bed, still higher when sitting on a chair, and highest when sitting and when inspiration on the well side was hindered, thus throwing a larger portion of the work on the diseased side, on which the measurements were made. During inspiration negative pressure increases in proportion to the depth of inspiration—or, in other words, in relation to the amount of expansion of the lungs—while during expiration it gradually falls to the standard at the beginning of inspiration. During forced inspiration it may reach  $-30$  to  $-40$  millimeters or more. The pressure thus observed within the thorax (*outside* of the lungs) is known as *intrathoracic* pressure, and must not be confounded with *intrapulmonary* or *respiratory* pressure, which exists *within* the lungs and the respiratory passages (see p. 408).

The thorax is capable of enlargement in all directions. It is cone-shaped, the top of the cone being closed in by the structures of the neck; the sides, by the vertebral column, ribs, costal cartilages, sternum, and intercostal sheets of muscular and other tissues; and the bottom, by the arched diaphragm. It is obvious that, since the thorax is an air-tight cavity and completely filled by various structures, enlargement in any direction must cause a diminution of pressure within the lungs, while a shrinkage would operate to bring about an opposite condition of increased pressure. Since the trachea is the only means of communication between the lungs and the atmosphere, it is evident that such alterations in pressure must encourage either the inflow or the outflow of air, as the case may be; consequently, when the thoracic cavity is expanded the pressure within the lungs is less than that of the atmosphere, and air is forced into the lungs; and when the thorax is decreased in size the reverse of the above pressure relation exists, and the air is expelled. In fact, the thorax and the lungs behave as a pair of bellows—just as air is drawn into the expanding bellows, so is air drawn into the lungs by the enlargement of the thorax; similarly, as the air is forced from the bellows by compression, so is air forced from the lungs by the shrinkage of the lungs and the thorax.

During the expansion of the thorax the lungs are entirely passive, and by virtue of their perfect elasticity merely follow the thoracic walls, from which they are separated only by the two layers of the pleuræ, which, being moistened with lymph, slide over each other without appreciable friction. That

<sup>1</sup> Virchow's Archiv, 1891, Bd. 126, S. 523.



the lungs are entirely passive is shown by the fact that when the thorax is punctured, so as to allow a free communication with the atmosphere, expansion of the chest is no longer followed by dilatation of the lungs. During the shrinkage of the thorax the elastic reaction of the lungs plays an active part.

**Respiration, Inspiration, and Expiration.**—Each respiration or respiratory act consists of an *inspiration* (enlargement of the thorax and inflation of the lungs) and an *expiration* (shrinkage of the thorax and the lungs). According to some observers, a *pause* exists after expiration (*expiratory pause*), but during quiet breathing no such interval can be detected. A pause may be present when the respirations are deep and infrequent. Under certain abnormal circumstances a pause may exist between inspiration and expiration (*inspiratory pause*).

Inspiration is accomplished by the contraction of certain muscles which are designated *inspiratory muscles*. Expiration during quiet breathing is essentially a passive act, but during forced breathing various muscles are active; these muscles are distinguished as *expiratory muscles*.

During inspiration the thorax is enlarged in the vertical, transverse, and antero-posterior diameters. During quiet breathing the vertical diameter is increased by the descent of the diaphragm, and during deep inspiration it is further increased by the backward and slightly downward movement of the floating ribs, and by the extension of the vertebral column, which raises the sternum with its costal cartilages and ribs. The transverse diameter is increased by the elevation and eversion (rotation outward and upward) of the ribs. The antero-posterior diameter is increased by the upward and outward movement of the sternum, costal cartilages, and ribs. During quiet inspiration in men the sternum is not raised to a higher level, but the lower end is rotated forward and upward. It is only during deep inspiration in men and in quiet or deep inspiration in women that the sternum as a whole is elevated.

The movements of the anterior and lateral walls constitute *costal* respiration, and those of the diaphragm *diaphragmatic* or, as it is sometimes called, *abdominal* respiration, since the descent of the diaphragm causes protrusion of the abdominal walls. Both types coexist during ordinary respiratory movements, but one may be more prominent than the other. The costal type is well marked in women, and the diaphragmatic type in men. These peculiarities are not, however, due to inherent sexual differences, but to dress. Young children of both sexes exhibit, as a rule, the diaphragmatic type, and it is only later, and owing to constricting dress, that the costal type is developed in the female.

The chief muscles of inspiration are the *diaphragm*, the *quadrati lumborum*, the *serrati postici inferiores*, the *scaleni*, the *serrati postici superiores*, the *levator costarum longi et breves*, and the *intercostales externi et intercartilaginei*.

**Movements of the Diaphragm.**—The *diaphragm* is attached by its two crura to the first three or four lumbar vertebræ, to the lower six or seven costal cartilages and adjoining parts of the corresponding ribs, and to the posterior surface of the ensiform appendix. It projects into the thoracic cavity in

the form of a flattened dome, the highest part being formed by the central tendon. The tendon consists of three lobes which are partially separated by depressions. The right lobe, or largest, is the highest portion and lies over the liver; the left lobe, which is the smallest, lies over the stomach and the spleen; while the central lobe is situated anteriorly, the upper surface blending with the pericardium. The central tendon is a common point of insertion of all the muscular fibres of the diaphragm. In the passive condition the lower portions of the diaphragm are in apposition to the thoracic walls. During contraction the whole dome is drawn downward, while the parts of the muscle in contact with the chest are pulled inward. According to Hultkranz, the cardiac part of the diaphragm descends from 5.5 to 11.5 millimeters during quiet inspiration, and as much as 42 millimeters during deep inspiration. Not only is the height of the arch lessened, but there is also a tendency, owing to the points of attachment of the diaphragm, toward the pulling of the lower ribs with their costal cartilages and the lower end of the sternum inward and upward; this traction, however, is counterbalanced by the pressure of the abdominal viscera, the latter being forced downward and outward against the thoracic and abdominal walls. If this counterbalancing pressure be removed by freely opening the abdominal cavity, especially after removing the viscera, the lower lateral portions of the thorax will be seen during each inspiration to be drawn inward. It is during labored inspiration only that this movement occurs in the intact individual.

When the diaphragm ceases to contract, the elastic recoil of the distended lungs is sufficient to draw the sunken dome upward into the passive position. This upward movement of the diaphragm is aided by the positive intra-abdominal pressure exerted by the elastic tension of the abdominal walls through the medium of the abdominal viscera. In forced expiration the contraction of the abdominal muscles (p. 407) adds additional force.

The *quadrati lumborum* are believed to assist the diaphragm by fixing the twelfth ribs, or even lowering and drawing them backward during deep inspiration. Each of these muscles arises from the ilio-lumbar ligament and the iliac crest, and is inserted into the transverse processes of the first, second, third, and fourth lumbar vertebrae and the lower border of one-half of the length of the last rib. These muscles are regarded by some physiologists as expiratory agents.

The *serrati postici inferiores* similarly assist the diaphragm by drawing the lower four ribs backward, and in deep inspiration also downward. They not only thus oppose the tendency of the diaphragm to pull the lower ribs upward and forward, which would lessen its effectiveness in enlarging the vertical diameter of the thorax, but they contribute to this enlargement by their backward and downward traction upon the ribs and the attached portions of the diaphragm. These muscles pass from the spines of the eleventh and twelfth dorsal and first two or three lumbar vertebrae and the supraspinous ligament to the lower borders of the ninth, tenth, eleventh, and twelfth ribs, beyond their angles.

Simultaneously with the contraction of the diaphragm the thoracic walls



are drawn upward and outward by the contractions of other inspiratory muscles, thus enlarging the thorax in the antero-posterior and lateral diameters.

**Movements of the Ribs.**—The movements of the ribs during inspiration are, as a whole, essentially rotations upward and outward upon axes which are directed obliquely outward and backward, each axis being directed through the costo-vertebral articulation and a little anterior to the costo-transverse articulation. The vertebral ends of the ribs lie higher than their sternal extremities, so that when the ribs are elevated the anterior ends are advanced forward and upward. The arches of the ribs are inclined downward and outward, and, owing to the obliquity of the axes of rotation, the convexities are rotated upward and outward, or everted. Thus both the antero-posterior and lateral diameters are increased.

The degree of obliquity of the axes of rotation of the different ribs varies. The axis of the first rib is almost transverse (Fig. 69), while that of each succeeding rib to the ninth, inclusive, becomes more oblique (Fig. 70). The

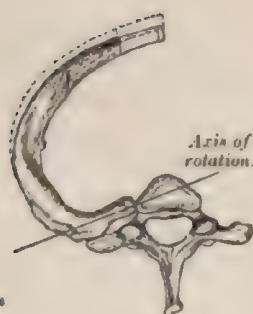


FIG. 69.—First dorsal vertebra and rib.

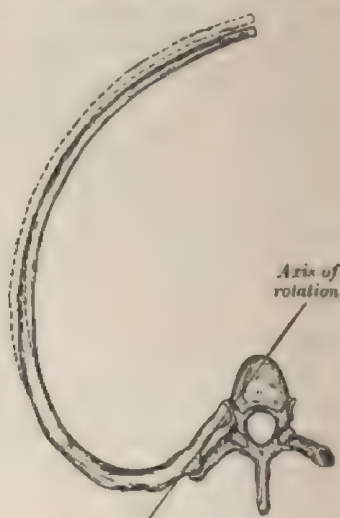


FIG. 70.—Sixth dorsal vertebra and rib.

more oblique the axis, the greater the degree of eversion; consequently the first rib is capable of but slight eversion, while the lower ribs may be everted to a relatively marked extent. Moreover, the peculiarities or the absence of the costo-transverse articulations materially affect the character of the movements of the different ribs. Thus, the facets on the transverse processes of the first and second dorsal vertebrae are cup-shaped, and into them are inserted the conical tuberosities of the ribs, thus materially limiting the rotation of the ribs; while the facets for the articulations of the third to the tenth ribs, inclusive, assume a plane character which admits of larger movement. The facets for the third to the fifth ribs are almost vertical, thus allowing a free movement upon the oblique axis; while the facets for the sixth to the ninth ribs, inclusive, are directed obliquely upward and backward, and admit of a move-

ment upward and backward as well as a rotation upon the oblique axis. Finally, the eleventh and twelfth ribs (and generally the tenth) have no costo-transverse articulations, allowing a movement backward and forward as well as rotation upon their oblique axes. While, therefore, the movements of the ribs are essentially rotations upward, forward, and outward upon oblique axes directed through the costo-vertebral articulations and a little anterior to the costo-transverse articulation, they are more or less modified by reason of the motion permitted by the nature or the absence of the costo-transverse articulations. Thus, the essential character of the movement of the first to the fifth ribs is a rotation upward, forward, and outward; that of the sixth to the ninth ribs, a rotation upward, forward, and outward combined with a movement upward and backward; that of the tenth and eleventh ribs, a rotation upward, forward, and outward with a rotation backward; that of the twelfth rib, chiefly a rotation backward and rather downward. The character of the movement of each rib differs somewhat as we pass from the first to the twelfth ribs.

During forced inspiration the sternum and its attached costal cartilages with their ribs are pulled upward and outward, while the ninth, tenth, eleventh, and twelfth ribs are drawn backward and downward. During expiration these movements are of course reversed.

The intercostal spaces during inspiration, except the first two, are widened.<sup>1</sup> The reason for this opening out must be apparent when we remember that the ribs are arranged in the form of a series of parallel curved bars directed obliquely downward, and the fact may be demonstrated by means of a very simple model (Fig. 71) consisting of a vertical support and two parallel bars, *a*, *b*, placed obliquely. If, after measuring the distance *c*, *d*, we raise the bars to a horizontal position, the distance *e*, *f* will be found to be greater than *c*, *d*, since the bars rotate around fixed points placed in the same vertical line. This widening of the intercostal spaces is readily accomplished because of the elasticity of the costal cartilages.

The muscles which may be involved in the movements of the ribs during quiet inspiration include the *scaleni*, the *serrati postici superiores*, the *levator costarum longi et breves*, and the *intercostales externi et intercartilaginei*.

The *scaleni* are active in fixing the first and second ribs, thus establishing, as it were, a firm basis from which the external intercostal muscles may act. The *scalenus anticus* passes between the tubercles of the transverse processes of the third, fourth, fifth, and sixth cervical vertebrae to the scalene tubercle on the first rib. The *scalenus medius* passes from the posterior tubercles of the transverse processes of the lower six cervical vertebrae to the upper surface of the first rib, extending from the tubercle to just behind the groove for the subclavian artery. The *scalenus posticus* passes from the transverse pro-

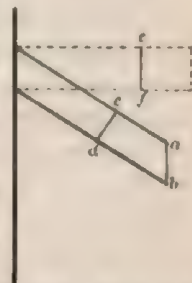


FIG. 71.—Model to illustrate the widening of the intercostal spaces during inspiration.

<sup>1</sup> Ebner: *Archiv für Anatomie und Physiologie*, Anatomische Abtheilung, 1886, S. 199.

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cesses of the two or three lower cervical vertebræ to the outer surface of the second rib.

The *serrati postici superiores* aid in fixing the second ribs and raise the third, fourth, and fifth ribs. The muscles pass from the ligamentum nuchæ and the spines of the seventh cervical and first two or three dorsal vertebræ to the upper borders of the second, third, fourth, and fifth ribs, beyond their angles.

The *levator costarum breves* consist of twelve pairs which pass from the tips of the transverse processes of the seventh cervical and first to the eleventh dorsal vertebræ downward and outward, each being inserted between the tubercle and the angle of the next rib below. Those arising from the lower ribs send fibres to the second vertebra below (*levator costarum longiores*). They assist in the elevation and eversion of the first to the tenth ribs, inclusive, and co-operate with the quadrati lumborum and the *serrati postici inferiores* to draw the lower ribs backward.

The functions of the *intercostales* have been a matter of dispute for centuries, and the problem is still unsettled. For instance, Galen looked upon the external intercostals as being expiratory. Vesalius asserted that both the external and the internal intercostals are expiratory, while Haller expressed the opposite belief. Hamberger and Hutchinson regarded the external intercostals and the interchondrals as being inspiratory, and the interosseous portion of the internal intercostals as being expiratory. Finally, Landois believes that while the external intercostals and the interchondrals are active during inspiration, and the interosseous portion of the internal intercostals during expiration, their chief actions are not to enlarge nor to diminish the volume of the thoracic cavity, but to maintain a proper degree of tension of the intercostal spaces. Each view still has its adherents.

The actions of the intercostal muscles are generally demonstrated by means of rods and elastic bands arranged in imitation of the ribs and the origins and insertions of the muscles, or by geometric diagrams. The well-known model of Bernoulli consists of a vertical bar representing the vertebral column, upon which bar move two parallel straight rods in imitation of the ribs (Fig. 72). If the rods be placed at an oblique angle and a tense rubber band (*a, b*) be affixed to represent the relations of the external intercostals, the rods will be pulled upward and the space between them will be widened. The interchondral portion of the internal intercostals bears the same oblique relation to the costal cartilages, and theoretically should have the same action. The action of the interosseous portion of the internal intercostals is demonstrated in this way: If the rubber band be placed at right angles to the rods (Fig. 73, *a, b*) and the rods be raised to a horizontal position, the rubber is put on the stretch (*c, d*), so that when the rods are released they will be pulled downward by the elastic reaction of the rubber. This last demonstration has been held to indicate that during inspiration the interosseous portion of the internal intercostals is put on the stretch and in an oblique position, and therefore in a relation favorable for effective action during contraction. The ribs, however, differ essentially from such a model in the fact that they are curved bars, that their

ends are not free, and that the movement of rotation is materially different. In fact, the mechanical conditions are so complex that deductions from phenomena observed in such gross demonstrations or by means of geometric figures such as suggested by Rosenthal and others must be accepted with caution.

There is no doubt that stimulation of any of the intercostal fibres causes an elevation of the rib below if the rib above be fixed, and that if the excitation be sufficiently strong and the area be large, the effect may extend from rib to rib, and thus a large part of the thoracic cage will be elevated. Consequently, it has been assumed that, should the upper ribs be fixed, the contractions of both sets of intercostals would elevate the system of ribs below. But the experiments of Martin and Hartwell<sup>1</sup> show that during forced inspiration the internal intercostals contract alternately with the diaphragm and the external intercostals, and therefore are expiratory. Moreover, Ebner<sup>2</sup> has found, as a result of elaborate measurements, that the intercostal spaces, excepting the first two, are, instead of being narrowed, actually widened during inspiration.

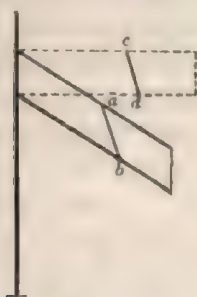


FIG. 72.—Model to illustrate the action of the external intercostals and interchondrals.

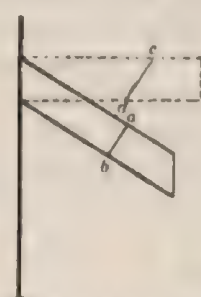


FIG. 73.—Model to illustrate the action of the interosseous portion of the internal intercostals.

An examination of the origins and insertions of the external intercostals and the interosseous portion of the internal intercostals, and of their actions during contraction, renders it apparent that it is possible for the externi to elevate the ribs and to widen the intercostal spaces, but that such effects are impossible in the case of the interosseous portion of the internal intercostals. Thus, if we take the model described above (Fig. 72), project a line *a, b* in imitation of the relation of the external intercostals to the ribs, and raise the parallel bars to a horizontal position, the distance between *c, d* is shorter than that between *a, b*. It is but a logical step from this demonstration to assume that, should a strip of muscle be placed between *a, b*, the muscle in *shortening* would pull the bars upward, at the same time widening the intercostal spaces. If now the upper ribs be fixed, it is obvious that the external intercostals must raise the ribs and open up the intercostal spaces during contraction. This same reasoning applies to the interchondrals, and the experiments of Hough<sup>3</sup> show that they contract synchronously with the diaphragm, and therefore with the external intercostals.

<sup>1</sup> *Journal of Physiology*, 1879-80, vol. 2, p. 24.

<sup>2</sup> *Loc. cit.*

<sup>3</sup> *Studies from the Biological Laboratory, Johns Hopkins University*, March, 1894.



In considering the interosseous portion of the internal intercostals we find that during the passive condition they are placed nearly at right angles to the ribs. If contraction takes place, it is obvious that the mechanical response must be an approximation of the ribs and a lessening of the width of the intercostal spaces. It must also be apparent that during the movement of inspiration these fibres are put on the stretch, which can be demonstrated in the above model. Thus, if we put a rubber band at right angles to the parallel rods (Fig. 73), we will find that when the rods are in the horizontal position, in imitation of the position of the ribs at the beginning of expiration, the distance between  $c, d$  is greater than that between  $a, b$ ; therefore if we lessen the distance between  $c, d$ , as when the muscle-fibres contract, the mechanical result of contraction must be approximation, the opposite to that which occurs during inspiration.

While the whole subject of the actions of the intercostal muscles must still be regarded as in an unsettled condition, yet there is no reasonable doubt that the externi and the intercartilaginei contract during inspiration, and the interosseous portion of the internal intercostals during expiration. Admitting this to be true, it is, however, by no means clear whether or not these muscles are for the purpose of altering the volume of the thorax. It is probable, as suggested by Landois, that their chief function is to maintain, during all phases of the respiratory movements, a proper degree of tension of the intercostal tissues. If this view be correct, the external intercostals and interchondrals contract during inspiration chiefly for the purpose of causing greater tension of the intercostal tissues, so as to counteract the influence of the increase of negative intrathoracic pressure; while during expiration, when their relaxation occurs, a substitution for this relaxation is provided by the contraction of the interosseous portion of the internal intercostals, so that the tension of the intercostal tissues is maintained. The internal intercostals must prove most effective during forced expiratory efforts—for example, in coughing, when the intercostal tissues are subjected to high positive intrathoracic pressure, and there is a consequent tendency to outward displacement, which is met and counteracted by the internal intercostals.

During forced inspiration the *scaleni* and the *serrati postici superiores* contract vigorously, so that the sternum and the first five ribs are elevated, thus raising the thoracic cage as a whole. At the same time the *serrati postici inferiores*, the *quadrati lumborum*, and the *sacro-lumbales* are active in pulling the lower ribs downward and backward. Besides these muscles there are a number of others which directly or indirectly affect the size of the thorax and which may be brought into activity; chief among these are the *sterno-cleido-mastoidei*, the *trapezei*, the *pectorales minores*, the *pectorales majores* (costal portion), the *rhomboidei*, and the *erectores spinæ*.

The *sterno-cleido-mastoid* passes from the mastoid process and the superior curved line of the occipital bone to the upper front surface of the manubrium and the upper border of the inner third of the clavicle. These muscles elevate the upper part of the chest when the head and neck are fixed. The

*trapezius* passes from the occipital bone, the ligamentum nuchæ, the spines of the seventh cervical and of all the dorsal vertebræ, and the supraspinous ligament to the posterior border of the outer third of the clavicle, the inner border of the acromion process, the crest of the spine of the scapula, and to the tubercle near the root. The trapezei help to fix the shoulders. The *rhomboid-eus minor* passes from the ligamentum nuchæ and the spines of the seventh cervical and first dorsal vertebræ to the root of the spine of the scapula. The *rhomboid-eus major* passes from the spines of the first four or five dorsal vertebræ and the supraspinous ligament to the inferior angle of the scapula. The trapezei and rhomboidei fix the shoulders, affording a base of action from which the pectorales act. The *pectoralis major* passes from the pectoral ridge of the humerus to the inner half of the anterior surface of the clavicle, the corresponding half of the anterior surface of the sternum, the cartilages of the first six ribs, and the aponeurosis of the external oblique muscle. The *pecto-ralis minor* passes from the coracoid process of the scapula to the upper margin and outer surface of the third, fourth, and fifth ribs close to the cartilages and to the intercostal aponeuroses. The pectorales minores and the costal portion of the pectorales majores raise the ribs when the shoulders are fixed. The *erectores spinæ* are composite muscles extending along each side of the spinal column, each consisting of the sacro-lumbalis, the musculus accessorius, the cervicalis ascendens, the longissimus dorsi, the transversalis cervicis, the trachelo-mastoid, and the spinalis dorsi. The erectores spinæ straighten and extend the spine and the neck, and thus tend to raise the sternum, the costal cartilages, and the ribs. The *infrahyoidei* may also be included among the muscles engaged in forced inspiration, since they may aid in the elevation of the sternum.

**Summary of the Actions of the Chief Muscles of Inspiration.**—During quiet inspiration the diaphragm contracts, thus increasing the vertical diameter of the thorax, its effectiveness being augmented by the associated actions of the *quadrati lumborum* and the *serrati postici inferiores*, the former fixing the twelfth ribs, and the latter fixing the ninth, tenth, eleventh, and twelfth ribs, and thus preventing the muscular slips of the diaphragm attached to these ribs from drawing them inward and upward and thus diminishing the cavity of the thorax. Coincidentally with the contractions of these muscles the *scaleni* fix the first and second ribs, and the *serrati postici superiores* aid in fixing the second ribs and elevate the third, fourth, and fifth ribs; the *intercostales externi et intercartilaginei* and the *levatorum costarum longi et breves* elevate and evert the first to the tenth ribs, inclusive, throwing the lower end of the sternum forward; and the *levatorum*, in conjunction with the *quadrati lumborum* and the *serrati postici inferiores*, aid in fixing the lower ribs and even draw them backward. The *intercostales externi* also serve to maintain a proper degree of tension of the intercostal tissues.

During forced inspiration the *scaleni* and the *serrati postici superiores* act more powerfully and thus raise the sternum with its attached costal cartilages and ribs, being assisted by the *sterno-cleido-mastoidei* and the *infrahyoidei* when the head and neck are fixed, and by the *pectorales majores et minores*



when the shoulders are fixed by the *trapezei* and the *rhomboidei*. The *erectores spinæ* further assist this action by extending the spinal column.

**Movements of Expiration.**—During quiet breathing expiration is effected mainly or solely by the passive return of the displaced parts. Normal expiration is therefore essentially a passive act, although it may be assisted by the contraction of the interosseous portion of the internal intercostals. The most important factors are unquestionably the elastic tension of the lungs, costal cartilages, intercostal spaces, and abdominal walls, together with the weight of the chest.

The lungs after quiet expiration are in a state of elastic tension equal to a pressure of +1.9 to +3.9 millimeters of mercury (see p. 397), which pressure during inspiration is increased in proportion to the depth of the movement. As soon, therefore, as the inspiratory muscles cease to contract, this tension comes into play, and, aided by elastic and mechanical reactions below noted, forces air from the lungs. This elasticity, and the facility with which the air is expelled, may be demonstrated by inflating a pair of excised lungs and then suddenly allowing a free egress of the air: collapse occurs with remarkable rapidity, with a force proportionate to the degree of distention. The elastic costal cartilages are similarly put on the stretch: the lower borders are drawn outward and upward and are thus twisted out of position, so that as soon as the inspiratory forces are withdrawn they must untwist themselves, further aiding the elastic reaction of the lungs. The intercostal spaces, excepting the first two, are widened and the tissues are stretched, and the diaphragm during its descent presses upon the abdominal viscera, rendering the abdominal walls tense. When, therefore, inspiration ceases the reaction of the tense and elastic intercostal tissues aids in bringing the chest into the position of rest, while the stretched abdominal walls press upon the abdominal viscera and thus force the diaphragm upward. Finally, the chest-walls by their weight tend to fall from the position to which they have been raised, adding thus another factor toward the elastic reaction of the lungs, costal cartilages, intercostal tissues, and abdominal walls.

Whether or not the interosseous portion of the internal intercostal muscles assists in expiration cannot be stated with positiveness. The fact that these muscles contract during the expiratory phase and that the contraction results in an approximation of the ribs leads to the belief that they are expiratory. But, as before stated (p. 404), this activity may be primarily for the purpose of maintaining a proper degree of tension of the intercostal tissues. In the dog these muscles are not active until dyspnoea appears, while in the cat they do not come into play until extreme dyspnoea has set in (Martin and Hartwell). These facts certainly militate against regarding them as active expiratory factors during quiet breathing, while during forced expiration they may with accuracy be considered as being in part at least expiratory in function. We are therefore justified in concluding that normal quiet expiration is essentially a passive act due to elastic reaction and to the mechanical replacement of displaced parts.

During forced expiration certain muscles may be active, the chief being the *intercostales interni interossei*, the *triangulares sterni*, the *musculi abdominales*, and the *levatores ani*. The *intercostales interni interossei* are probably active expiratory muscles during forced expiration, but they can prove effective only when the lower part of the thoracic cage is fixed or drawn down—an act which is accomplished chiefly by the abdominal muscles.

The *triangulares sterni* pass outward and upward from the lower part of the sternum, the inner surface of the ensiform cartilage, and the sternal ends of the costal cartilages of the two or three lower sternal ribs, to the lower and inner surfaces of the cartilages of the second to the sixth ribs, inclusive. They draw the attached costal cartilages downward during expiration.

The *abdominales* during quiet expiration are passive, and aid in the expulsion of air from the lungs simply by their elasticity; but during forced expiration, by contraction, they are active expiratory factors.

The *obliquus externus* arises by slips on the outer surface and lower borders of the lower eight ribs, and is inserted into the outer lip of the anterior half of the crest of the ilium and into the broad aponeurosis which blends with that of the opposite side in the linea alba. The *obliquus internus* passes from the outer half or two-thirds of Poupart's ligament, the anterior two-thirds of the middle lip of the crest of the ilium, and the posterior layer of the lumbar fascia to the cartilages of the last three ribs and the aponeurosis of the anterior part of the abdominal wall. The *rectus abdominis* passes from the crest of the pubes and the ligaments in front of the symphysis pubis to the cartilages of the fifth, sixth, and seventh ribs, and usually to the bone of the fifth rib. The *transversalis abdominis* passes from the outer third of Poupart's ligament, the anterior three-fourths of the inner lip of the iliac crest, by an aponeurosis from the transverse and spinous processes of the lumbar vertebrae, and from the inner surface of the sixth lower costal cartilages to the pubic crest and the linea alba. The fibres for the most part have a horizontal direction. The *pyramidalis* passes from the anterior surface of the pubes and the pubic ligament to the linea alba. It is obvious from the points of origin and insertion of the abdominal muscles that during contraction they co-operate toward diminishing the volume of the thorax in three ways: (1) By offering a base of action for the internal intercostals, and thus aiding in the approximation of the ribs; (2) by depressing and drawing inward the lower end of the sternum and the lower costal cartilages and ribs; (3) by forcing the abdominal viscera against the diaphragm, thrusting it upward. The abdominales are unquestionably the chief expiratory muscles.

The *levatores ani* converge from the pelvic wall to the inner part of the rectum and the prostate gland. They form the largest part of the muscular floor of the pelvic cavity. The levatores ani are important during forcible expiration by resisting the downward pressure of the pelvic viscera caused by the powerful contractions of the abdominal muscles, but they must be regarded rather as associated in the act of expiration, and not as true expiratory muscles.

**Summary of the Actions of the Chief Muscles of Expiration.**—During



*quiet expiration* no muscular factors are involved, unless it be the contraction of the *intercostales interni interossei*, in which event they are more probably engaged in maintaining the tension of the intercostal tissues than in actually diminishing the capacity of the thorax.

During *forced expiration* the *abdominales* flex the thorax upon the pelvis, force the abdominal viscera against the diaphragm, thrusting it upward, and by pulling upon the lower margins of the thoracic cage draw them inward and at the same time offer a base from which the *intercostales interni interossei* act to pull the ribs downward; the *triangulares sterni* contract at the same time and pull downward the cartilages of the second to the sixth ribs, inclusive.

**Associated Respiratory Movements.**—Associated with the thoracic and abdominal movements of respiration are movements of the face, pharynx, and larynx. The nostrils are slightly dilated during inspiration and passively return to their condition of rest during expiration; the soft palate moves to and fro with the inflow and outflow of air, and the glottis is widened during inspiration and narrowed during expiration. During labored inspiration, besides the above movements, the mouth is usually opened; the muscles concerned in facial expression may be active, giving the individual an appearance of distress; the soft palate is raised, and the larynx descends. The widening of the nares and the glottis, the opening of the mouth, the elevation of the soft palate, and the descent of the larynx during inspiration are obviously for the purpose of lessening the resistance to the inflow of air.

**Intrapulmonary or Respiratory Pressure and Intrathoracic Pressure.**—The tidal flow of air to and from the lungs during the respiratory movements is due, as already stated, to the differences between the pressure within the lungs and that outside the body. During inspiration the enlargement of the thorax causes an expansion of the lungs and a consequent diminution of pressure within them, so the air is forced through the air-passages until the pressure within the lungs equals that of the atmosphere; during expiration there occur elastic and mechanical reactions whereby the pressure within the lungs is greater than that of the atmosphere, consequently air is expelled until an equilibrium is again established. It is apparent, then, that during inspiration there exists within the lungs a condition of *negative* pressure, and that during expiration the pressure is *positive*. If a manometer be so arranged as in no way to interfere with the ingress and egress of air, it will be found that during inspiration the column of mercury sinks, while during expiration it rises. Donders found by connecting a manometer with the nasal passage that the pressure during quiet inspiration was  $-1$  millimeter of Hg, and during expiration  $+2$  to  $3$  millimeters. Ewald gives as corresponding values  $-0.1$  millimeter and  $+0.13$  millimeter, and Mundhorst,  $-0.5$  millimeter and  $+5$  millimeters. During deep inspiration Donders noted a pressure of  $-30$  millimeters, and when the mouth and nose were closed,  $-57$  millimeters. During forced expiration, with respiratory passage closed, it was  $+87$  millimeters; but these figures have been exceeded.

It will be observed that during quiet respiration intrapulmonary pressure (pressure *within* the lungs) oscillates between negative and positive and *vice versa*, whereas intrathoracic pressure (pressure *outside* the lungs) is persistently negative, the amount by which it differs from atmospheric pressure becoming greater during inspiration and diminishing to the previous level during expiration (p. 397). Under forced expiration, however, when the air-passages are obstructed intrathoracic pressure may become positive. This may be demonstrated in this way: If a manometer be connected with the mediastinum of a cadaver, and the chest be pulled upward in imitation of deep inspiration, intrathoracic pressure will be found to be about  $-30$  millimeters. If now a second manometer be connected with the trachea, and air be forced into the lungs through a tracheal tube, as intrapulmonary pressure rises intrathoracic pressure falls, so that when the former reaches  $+30$  millimeters the intrathoracic negative pressure exerted by the elastic traction of the lungs is counterbalanced and the pressure within and outside the lungs is equal. If intrapulmonary pressure now rise above this limit, intrathoracic pressure must proportionately become positive. During violent coughing, when the expiratory blast is obstructed and the muscular effort is powerful, intrapulmonary pressure may rise to  $+80$  millimeters or more.

The intercostal tissues tend to be drawn inward as long as negative intrathoracic pressure exists, and to be forced outward when there is positive intrathoracic pressure; hence during inspiration the traction becomes more marked with the rise of intrathoracic pressure, and during expiration the reverse; while during forced expiration with obstructed air-passages the pressure exerted by the effort of the expiratory muscles, together with the weight of the chest and the elastic reaction of the costal cartilages, etc., may be, as above stated, far more than sufficient to counterbalance the traction exerted by the distended elastic lungs, and thus cause positive intrathoracic pressure.

The influences exerted by changes in intrathoracic and intrapulmonary pressure upon the circulation are marked and important, and may be so pronounced as to cause an obliteration of the pulse.

**Respiratory Sounds.**—During the respiratory acts characteristic sounds are heard in the lungs. A study of these sounds, however, properly belongs to physical diagnosis.

**The Value of Nasal Breathing.**—Nasal breathing has a value above breathing through the mouth, inasmuch as the air is warmed and moistened and thus rendered more acceptable to the lungs, more or less of the foreign particles in the air are removed, and noxious odors may be detected.

#### B. THE GASES IN THE LUNGS, BLOOD, AND TISSUES.

**Alterations in the Gases in the Lungs.**—The object of respiratory movements is to renew the air within the lungs, which air is constantly being vitiated, and thus supply  $O$  and remove  $CO_2$  and other effete substances. The lungs of the average adult man after quiet expiration contain about 2800 cubic centimeters (170 cubic inches) of air. During quiet respiration there is an



inflow and outflow of about 500 cubic centimeters (30 cubic inches), therefore from one-sixth to one-fifth of the air in the lungs is renewed by each act. Since the respirations occur at so frequent a rate as 16 to 20 per minute, it seems apparent that there must be a rapid loss of O and a gain of CO<sub>2</sub>. This is proven by analyses of inspired and expired air. Inspired air is under normal circumstances atmospheric air, composed of oxygen, nitrogen, argon, and carbon dioxide, with more or less moisture, traces of ammonia and nitric acid, dust and micro-organisms, etc. The essential differences between inspired and expired air are shown by the following table, the figures for the gases being in volumes per cent. Nitrogen and argon are omitted because they play no important rôle in respiration, there being neither absorption nor discharge of either to any noteworthy extent. They take no part, as far as known, beyond that of a mere diluent of the inspired and expired air.

	O	CO <sub>2</sub>	Water Vapor.	Temperature.	Volume (Actual).
Inspired air . . . . .	20.81	0.04	Variable.	Average about 20°	
Expired air . . . . .	16.03	4.38	Saturated.	Average, about 36.3°	Diminished
	4.78	4.34			$\frac{1}{2}$ to $\frac{1}{3}$ .

Expired air is therefore 4.78 volumes per cent. poorer in O, 4.34 volumes per cent. richer in CO<sub>2</sub>; it is saturated with water vapor, and is of higher temperature and of less actual volume. In addition, expired air contains various effete bodies, such as organic matter, hydrogen, marsh-gas, etc.

The relative quantities of O absorbed and of CO<sub>2</sub> given off are not constant, and the ratio is known as the *respiratory quotient*. This is obtained by dividing the volume of CO<sub>2</sub> given off by that of O absorbed,  $\frac{\text{CO}_2, 4.34}{\text{O}, 4.78} = 0.908$ . Hence, for each volume of O that is lost 0.908 volume of CO<sub>2</sub> is gained. Various conditions affect the quotient (p. 436).

The quantity of watery vapor lost by the lungs varies inversely with the amount contained in the atmosphere and with the volume of air respired. The less the moisture in the atmospheric air and the larger the volume of air respired, the greater the loss. Valentine, in experiments on eight young men, records a daily loss varying from 349.9 to 773.3 grams, or an average of 540 grams. Vierordt records a loss of 330 grams, while Aschenbrandt estimates a daily loss of 526 grams.

The temperature of the expired air varies directly with the temperature and volume of the inspired air and with the temperature of the body. Valentine and Bruner found that when the temperature of inspired air was from 15° to 20°, that of expired air was 37.3°; when that of inspired air was -6.3°, expired air had a temperature of 29.8°; while when the inspired air was at 41.9°, that of expired air was 38.1°. When the air is respired through the nose the expired air is warmer than when respiration occurs through the mouth. Bloch<sup>1</sup>

<sup>1</sup> *Zeitschrift für Ohrenheilkunde*, 1888, Bd. xviii. S. 215.

records a difference of  $1.5^{\circ}$  to  $2^{\circ}$ . The figures by other observers vary from  $0.5^{\circ}$  to  $1.5^{\circ}$ . The larger the volume of air respired, other things being equal, the less the increase of temperature.

The volume of expired air is from 10 to 12 per cent. greater than that of inspired air, this increase being due to expansion caused by the increase of temperature. When dried and proper deductions made for temperature and barometric pressure, the actual or corrected volume is less by about  $\frac{1}{40}$  to  $\frac{1}{80}$ .

Lossen estimated that 0.0204 gram of ammonia is eliminated per diem in the expired air. Bergey also found small quantities of ammonia, yet Voit's investigations indicate that expired air usually does not contain even a trace of ammonia.

**Alterations in the Gases in the Blood.**—The blood in the pulmonary artery is of the typical venous color—that is, deep bluish-red. During its passage through the lungs it becomes scarlet-red, or, commonly speaking, arterialized or aërated. If we take arterial blood and deprive it of oxygen, the color changes to a venous hue; if now we shake the bluish-red blood in air or O, the scarlet-red color is restored. We have here the suggestion that the blood while passing through the lungs absorbs O. Analyses show that not only does absorption of O occur, but that there is simultaneously with this an elimination from the blood of  $\text{CO}_2$ .

Arterial and venous blood each contains approximately 60 volumes per cent. of O and  $\text{CO}_2$ ; that is, for about every 100 volumes of blood 60 volumes of gas will be obtained. Such analyses demonstrate also that while the total volumes per cent. of O and  $\text{CO}_2$  are about the same, the proportions are different. The following table, compiled from various sources, gives the volumes per cent. of gases in the arterial blood of various animals:

Animal	Total	O.	$\text{CO}_2$ .	N.
Dog . . . . .	59.38	18.65	38.93	1.8
Cat . . . . .	48.2	13.1	28.8	1.3
Sheep . . . . .	57.6	10.7	45.1	1.8
Rabbit . . . . .	49.3	13.2	34.0	2.1
Man . . . . .	63.4	21.6	40.3	1.5
Fowl . . . . .	58.8	10.7	48.1	

Pflüger obtained as averages of analyses of arterial blood of dogs 58.3 volumes per cent., consisting of 22.2 volumes per cent. of O, 34.3 volumes per cent. of  $\text{CO}_2$ , and 1.8 volumes per cent. of N. Venous blood, according to estimates by Zuntz based on a large number of analyses, contains 7.15 volumes per cent. less of O and 8.2 volumes per cent. more of  $\text{CO}_2$ . The quantity of N is practically the same in both arterial and venous blood.

The proportions of O and  $\text{CO}_2$  in arterial blood vary but little in specimens taken at random from the arterial system, while those of venous blood, on the contrary, differ considerably according to the locality of the vessel as well as to the degree of activity of the structures whence the blood comes. Thus, venous blood from an active secreting gland differs very little in its composition, gaseous and otherwise, from typical arterial blood, whereas when



the gland is inactive the blood is typically venous. The arterial character of the venous blood in the former case is due to the considerable increase in the quantity of blood passing through the gland during activity, the result being that the loss and gain of substances are not so noticeable although the total quantities of O and CO<sub>2</sub> and other substances exchanged are actually greater than when the gland is at rest and the blood coming from it has the typical venous characters.

The venous blood during its passage through the lungs acquires O and loses CO<sub>2</sub>. After the blood is arterialized it passes from the lungs into the left side of the heart, from which it is forced to the aorta and its ramifications and ultimately into the capillaries. Here it undergoes a retrograde change, parting with some of its O and taking in exchange CO<sub>2</sub>; consequently the gaseous interchange between the blood and the tissues is the reverse of that occurring between the blood and the air. Thus we find that the interchange of O and CO<sub>2</sub> occurs in a distinct series of events: (1) Oxygen is carried as a constituent of the atmospheric air to the alveoli; (2) here it is absorbed by the venous blood, which at the same time gives off CO<sub>2</sub> to the air in the alveoli; (3) O is now in major part conveyed to the tissues, in which it is taken up and utilized in processes of oxidation, CO<sub>2</sub> being the chief effete product, which is formed immediately or ultimately and given to the blood (a part of the O is consumed by the blood, CO<sub>2</sub> being one of the results); (4) the venous blood is now conveyed to the lungs, CO<sub>2</sub> is given off and O is received in exchange, and the series of events is repeated.

**The Forces Concerned in the Diffusion of O and CO<sub>2</sub> in the Lungs.**—If the air expired be collected in a number of parts, each successive portion will be found to contain a smaller percentage of O and a larger percentage of CO<sub>2</sub>. The air in the beginning of the respiratory tract (nose and mouth) varies from atmospheric air but little in composition, while that in the alveoli contains considerably less O and much more CO<sub>2</sub>. With each quiet act of inspiration the quantity of air breathed is from three to four times greater than the capacity of the trachea and bronchi, so that with each respiratory act two-thirds or more of the fresh air is carried into the alveoli. When expiration occurs a similar volume of the vitiated air within the alveoli is driven into the bronchi and trachea, and thus a certain percentage is expelled from the body. Thus the mere volume and force of the air-currents must obviously be of great value in equalizing the composition of the air in the different parts of the respiratory tract.

The contractions of the heart exert similar mechanical influences. With each contraction intrathoracic pressure is lessened, so that there is a slight expansion of the lungs, just as would be caused had the thorax been slightly enlarged, and consequently there is a movement of air toward and into the alveoli. During diastole intrathoracic pressure returns to the previous level, the volume of the lungs is diminished, and the air is driven from the alveoli. Thus each heart-beat causes a to-and-fro movement of the air. These oscillations, which are termed *cardio-pneumatic movements*, are of more importance than might seem at first sight, for it has been shown that in cases of suspended

animation and in hibernating animals they aid materially in pulmonary ventilation.

Besides these mechanical factors there is present the important factor of the diffusion of gases, O diffusing toward the alveoli and CO<sub>2</sub> toward the anterior nares. The rapidity with which diffusion occurs, other things being equal, depends upon the differences in the "partial pressure" of the gas at various regions. Each gas forming part of a mechanical mixture exerts a partial pressure proportional to its percentage of the mixture. Thus, atmospheric air contains 20.81 volumes per cent. of O, 0.04 volumes per cent. of CO<sub>2</sub>, and 79.15 volumes per cent. of N. If the air exists at 760 millimeters barometric pressure, each gas will exert a *part* of the total pressure, or a "partial pressure," equivalent to its respective volume. Should we wish to find the partial pressure of O, it may be ascertained simply by taking  $\frac{20.81}{100}$  of the total pressure =  $\frac{20.81 \times 760}{100}$  = 158.15 millimeters; similarly, the partial pressure of CO<sub>2</sub> would be  $\frac{0.04 \times 760}{100}$  = 0.30 millimeter; and that of N,  $\frac{79.15 \times 760}{100}$  = 601.54 millimeters. Knowing, then, the composition of any mixture of gases and the total pressure under which it exists, it is a matter of very simple calculation to determine the partial pressure of each of the various gases constituting the atmosphere. Expired air is poorer in O and richer in CO<sub>2</sub> than inspired air, and alveolar air is altered even to a greater extent than expired air; hence the partial pressures must be affected similarly.

The first portion of the air expired contains a maximum amount of inspired air and a minimum amount of the air contained in the air-passages previous to the inspiratory act; but as expiration continues the mixture becomes poorer and poorer in inspired air and similarly richer in the vitiated air from the smaller air-passages and the alveoli; in fact, the last portion of expired air is very similar to, if not identical in its composition with, that in the alveoli. The following partial pressures of O and CO<sub>2</sub> in inspired air and alveolar air indicate the extent to which the composition varies in different parts of the respiratory tract:

Gas	Inspired Air.	Alveolar Air.
O . . . . .	158.15 millimeters.	100 millimeters. <sup>1</sup>
CO <sub>2</sub> . . . . .	0.30 millimeter.	23 millimeters.

Since the partial pressure of O in inspired air is about 158.15 millimeters, and as it is but about 100 millimeters in the alveoli, and as the air is poorer in O as we pass from the nares to the alveoli, it is obvious that a force must be exerted constantly to cause a diffusion of O from the larger air-passages to the bronchioles and from the bronchioles to the alveoli—that the O must diffuse from the region of highest pressure to that of lowest pressure. During life an equilibrium can never be established, because of the constant supply of fresh air and the continual passage of O from the alveoli to the blood. The

<sup>1</sup> The exact per cent. composition of alveolar air is not known; these figures are estimates.



same relations of partial pressure are observed in connection with  $\text{CO}_2$ , except that the air in the alveoli is incessantly acquiring this gas from the blood, causing the per cent. composition of  $\text{CO}_2$  to be much in excess of that found in the atmosphere. The partial pressure of  $\text{CO}_2$  in the alveolar air is about 23.00 millimeters, while in inspired air it is only 0.30 millimeter; hence  $\text{CO}_2$  must diffuse from the alveoli outward.

There are, therefore, three important factors concerned in the admixture and purification of the air in the lungs: (1) The tidal movements caused by inspiration and expiration, which movements by the mere force of air-currents cause a partial mixture of the air; (2) the smaller wave-movements (cardio-pneumatic) produced by the heart-beats, and similar in effect to, but much less effective than, the first; (3) the diffusion of O and  $\text{CO}_2$ , depending upon differences in their partial pressures in the various parts of the respiratory tract. The first is by far the most important.

**The Forces Concerned in the Interchange of O and  $\text{CO}_2$  between the Alveoli and the Blood.**—The gases in the lungs are in the form of a mechanical mixture, while in the blood they are in solution or in chemical combination; hence we now have to deal with conditions quite different, involving the consideration of the relations of gases to liquids—a relationship of twofold nature, inasmuch as the gas may be found not only in solution, but in chemical association.

When an atmosphere consisting of O,  $\text{CO}_2$ , and N is brought in contact with water, each gas is absorbed independently not only of the others, but of the nature and quantity of all other gases which may happen to be in solution. The quantity of each gas dissolved depends upon its relative solubility as well as upon the temperature and the barometric pressure. The coefficient of absorption of any fluid is the quantity of gas dissolved at a given temperature and pressure, and is in inverse relation to temperature and in direct relation to pressure. The following absorption-coefficients of water for O,  $\text{CO}_2$ , and N at 760 millimeters of Hg have been obtained by Winkler:<sup>1</sup>

Temperature.	O.	$\text{CO}_2$ .	N.
0° . . . . .	0.04890	1.7967	0.02348
15° . . . . .	0.03415	1.0020	0.01682
40° . . . . .	0.02306	...	0.01183

Thus, at 0° C and 760 millimeters pressure each volume of water absorbs 0.0489 volume of O; at 15°, 0.03415 volume; and at 40°, 0.02306 volume. The absorption-coefficient falls, it will be observed, with the increase of temperature. Comparing the solubilities of the three gases, it will be seen that at the same temperature and pressure a considerably larger quantity of  $\text{CO}_2$  is absorbed than of O—nearly forty times more—whereas the quantity of N absorbed is less than one-half as much as that of O.

The quantity of a gas absorbed by a given liquid at a given temperature is proportionate to its coefficient of solubility and to the pressure, and is the same

<sup>1</sup> *Zeitschrift für physikalische Chemie*, 1892, Bd. 9, S. 173.

whether the gas exist free or as a constituent of a complex atmosphere, provided that the pressure exerted by the gas in both cases be the same. Thus, atmospheric air consists of 20.81 volumes per cent. of O, 0.04 volume per cent. of CO<sub>2</sub>, and 79.15 volumes per cent. of N. Each gas exerts a partial pressure in proportion to its percentage of the mixture. Assuming that the air is at standard atmospheric pressure, the partial pressure of O is 20.81 per cent. of 760 millimeters of Hg, or 158.15 millimeters. The quantity of O absorbed from the air at 0° C and 760 millimeters pressure is therefore the same as when the atmosphere consists of pure O at a pressure of 158.15 millimeters.

The absorption-coefficient must consequently be  $\frac{20.81 \times 0.0489}{100} = 0.01$  volume. Therefore 100 volumes of water at 0° C. and 760 millimeters pressure absorb from the air 1 volume of O.

If the partial pressure of O be increased or decreased, the quantity absorbed will rise or fall accordingly. From this it is obvious that O must exist under a certain degree of pressure to prevent its passing out of solution, which is expressed by the term *tension* of solution, meaning, in a word, the pressure required to keep the gas in solution. If the partial pressure of the gas diminishes, the gas in solution is given off until the *partial pressure* of the gas in the air and the *tension* of the gas in solution are equal. Conversely, as the partial pressure of the gas in the air increases, the gas in solution will be under correspondingly higher tension.

*Tension of O.*—The absorption-coefficient of blood for O is nearly the same as that of water, so that blood at 0° should absorb from the atmosphere about 1 volume per cent. of O, but less than one-half as much at the temperature of the body. The results of experiments show, however, that blood contains considerably more than this (see table, p. 411), and very much more than can be accounted for by the laws of partial pressures and tensions. Moreover, when the blood is subjected to a vacuum pump there is evolved a small amount of gas consistent with the diminution of pressure, but the great bulk of it does not come off until the pressure has been reduced to  $\frac{1}{30}$  to  $\frac{1}{10}$  of an atmosphere. Finally, the quantity absorbed is affected but little by changes in pressure above or below a certain standard. These facts indicate that almost all of the O must be in chemical combination. This combination is with hæmoglobin in the form of oxyhæmoglobin. This chemical union is readily dissociated at a constant minimal pressure which is termed the *tension of dissociation*. There is a persistent tendency of the gas in such a compound to become disengaged, so that when oxyhæmoglobin is placed under circumstances where the tension or the partial pressure of O is less than that in the compound dissociation occurs; conversely, when hæmoglobin is brought in contact with O at a pressure above the minimal constant of dissociation ( $\frac{1}{30}$  to  $\frac{1}{10}$  of an atmosphere), the two unite to form oxyhæmoglobin. One gram of hæmoglobin from ox blood combines, according to Hüfner,<sup>1</sup> with 1.34 cubic centimeters of O at 0° and 760 millimeters pressure. Assuming

<sup>1</sup> *Archiv für Anatomie und Physiologie*, 1894, S. 130.



that 100 cubic centimeters of blood contain 15 grams of hæmoglobin (p. 37), the quantity of gas which would combine with this amount of hæmoglobin would be equal to 20.1 cubic centimeters; in other words, arterial blood should contain, if the hæmoglobin be saturated with oxygen, 20.1 volumes per cent. of O.

The plasma and the serum absorb but very small quantities of O—according to Pflüger, only 0.26 volume per cent. Owing to the relatively low absorption-coefficient of the plasma compared with the O-capacity of the hæmoglobin, as well as to the fact that the hæmoglobin is nearly saturated at a relatively low pressure, the quantity of O absorbed is not materially affected by an increase of pressure above the level of the tension of dissociation.

The tension of O in arterial and venous blood must be ascertained separately, inasmuch as each contains a different percentage. Following this method, Strassburg<sup>1</sup> records the following averages: Arterial blood, 29.64 millimeters of Hg, or 3.9 per cent. of an atmosphere; and venous blood, 22.04 millimeters, or 2.9 per cent. of an atmosphere. The figures obtained by Bohr and by Haldane and Smith<sup>2</sup> are, however, much higher (see p. 418).

*Tension of CO<sub>2</sub>.*—Venous blood contains about 45 volumes per cent. of CO<sub>2</sub>. The results of experiments prove that only about 5 per cent. of this CO<sub>2</sub> is in simple solution, that from 10 to 20 per cent. is in firm chemical combination, and that from 75 to 85 per cent. is in loose combination.

When the blood at the temperature of the body is subjected to a vacuum, all of the CO<sub>2</sub> is given off; but if the blood-corpuscles be removed and the plasma and corpuscles each in turn be submitted to the pump, both will give off CO<sub>2</sub>, the plasma yielding a larger volume than the corpuscles, but not so much as when they are together. Plasma and serum *in vacuo* give off only a portion of their CO<sub>2</sub>; the remainder may, however, be dissociated by adding acid or red corpuscles. The red corpuscles therefore act as an acid and cause the disengagement of all the gas from the plasma; consequently, not only do the corpuscles yield up the CO<sub>2</sub> contained in them, but they are also active agents in bringing about the dissociation of CO<sub>2</sub> which is in chemical combination in the plasma. The dissociation is due in part, perhaps, to the presence of phosphates in the stromata of the red corpuscles, and to certain proteids, but the observations of Preyer and Hoppe-Seyler lead to the conviction that it is due chiefly to oxyhæmoglobin and hæmoglobin. While phosphates, proteids, hæmoglobin, and oxyhæmoglobin all may have the power of expelling CO<sub>2</sub> from sodium carbonate in solution *in vacuo*, this fact leaves us none the wiser as to which, if any, is active in this way in the blood. Arterial blood gives off its CO<sub>2</sub> more readily than venous blood.

Of the total quantity of CO<sub>2</sub>, about 5 per cent. is in simple solution and from 10 to 20 per cent. is in firm chemical combination in the plasma, the latter requiring the addition of acid or of hæmoglobin, etc. to cause its dissociation *in vacuo*; while the remainder, constituting much the larger proportion, is in

<sup>1</sup> *Archiv für Physiologie*, Bd. vi. S. 65.

<sup>2</sup> *Journal of Physiology*, 1897, vol. xxii. p. 231.

loose chemical union in both the plasms and the corpuseles. That which is in chemical combination in the plasma is probably in part combined with globulin and alkali, and in part with sodium as carbonate and bicarbonate, the proportion of each varying with the tension of the  $\text{CO}_2$ . The white blood-corpuseles, so far as they contain any of the  $\text{CO}_2$ , hold it probably in combination with globulin and an alkali, and as carbonates of sodium. The great bulk of the gas disengaged from the corpuseles is derived from the red cells, but in what combination or combinations it exists is not positively known. The experiments of Setschenow, Zuntz, Bohr,<sup>1</sup> and others indicate that it is associated in some obscure way with hæmoglobin which seems to have the power of combining with  $\text{CO}_2$ . This latter fact has been shown by the experiments of Bohr, who compared the quantities of  $\text{CO}_2$  absorbed by pure water and by solutions of pure crystallized hæmoglobin at constant temperature and varied pressure. He found that the weight of  $\text{CO}_2$  absorbed by the water increased regularly with the increase of pressure, whereas the quantity absorbed by the solution of hæmoglobin was very large relatively to the lower pressures and small for higher pressures, and that the increments of absorption were in decreasing ratio to the rise of pressure. The absorption curve is therefore steep at first, becoming less and less so with the increase of pressure, and entirely different from the absorption line for pure water, which is straight. Moreover, the quantity of  $\text{CO}_2$  dissolved was considerably in excess of that which physical laws could permit. It is not improbable that the O combines with the pigment portion of the hæmoglobin, and the  $\text{CO}_2$  with the proteid portion. The  $\text{CO}_2$ , in whatever form or forms it may exist in the red corpuseles, is in looser combination than in serum.

Strassburg's experiments show that the average tension of  $\text{CO}_2$  in arterial blood is 21.28 millimeters of Hg, or 2.8 per cent. of an atmosphere, and in venous blood 41.04 millimeters, or 5.4 per cent. of an atmosphere.

*Tension of N.*—The quantity of nitrogen in the blood is about 1.8 volumes per cent. It is in simple solution in the blood-plasma, and the quantity in both venous and arterial blood is practically the same. Its presence and quantity are not of physiological importance. Argon has been found in the blood of the horse by Regnard and Th. Schlösing Sohn.<sup>2</sup>

**The Interchange of O and  $\text{CO}_2$  between the Alveoli and the Blood.**—Let us now inquire into the factors which bring about the passage of O from the alveoli to the blood and of  $\text{CO}_2$  from the blood to the alveoli. If we have two mixtures of the same gases, but in unlike proportions, and separate them by means of an animal membrane, diffusion will occur through the membrane until the partial pressures of the two gases are the same on the two sides of the membrane. Now modify this experiment by bringing an atmosphere of air in contact with water containing O,  $\text{CO}_2$ , and N in solution or in chemical combination: if the partial pressure of O in the air be greater than the tension

<sup>1</sup> *Exper. Untersuch. u. d. Sauerstoffaufnahme d. Blutfarbstoffes*, Kopenhagen, 1885; *Beiträge zur Physiology*, Festschr. f. C. Ludwig, 1887, pp. 164-174.

<sup>2</sup> *Comptes rendus de l'Acad. des Sci.*, 1897, t. 124, p. 302.



of O in the water, O will pass to the water; if the partial pressure of CO<sub>2</sub> in the air be less than the tension of CO<sub>2</sub> in the water, CO<sub>2</sub> will pass to the air. If now we interpose an animal membrane between the atmosphere and the water, the interchange of gases will continue as before. In this case we have conditions analogous to those which exist in the living organism: In the alveoli there is an atmosphere consisting of O, CO<sub>2</sub>, and N; each gas is under a partial pressure proportional to its volume per cent. of the mixture; the pulmonary membrane and the walls of the capillaries may be regarded as a simple animal membrane separating the air in the alveoli from the blood; finally, the blood contains O, CO<sub>2</sub>, and N, each of which exists under a definite and independent degree of tension. Whether or not any or all of these gases will pass in one direction or the other must obviously depend upon the conditions of partial pressure and tension of each gas on the two sides of the membrane. The tension of O in venous blood, as above stated, is 22.04 millimeters of Hg, and of CO<sub>2</sub>, 41.04 millimeters. What are the partial pressures of these gases in the alveoli? The precise pressures are not known, but it is estimated that the partial pressure of O is about 100 millimeters, and of CO<sub>2</sub> about 23 millimeters.

Comparing the partial pressures and the tensions, as generally accepted, of these two gases in the alveoli and the blood respectively, it is obvious that the conditions on the two sides of the membrane are favorable to the diffusion of O and CO<sub>2</sub>, and in definite but opposite directions. This is illustrated in the following diagrammatic presentation:

	O.	CO <sub>2</sub> .
Partial pressures in alveolar air . . . . .	100.00	23.00
Pulmonary membrane . . . . .	↓	↑
Tensions in venous blood . . . . .	22.04	41.04

Since gases diffuse from the point of higher pressure or tension to that of lower pressure or tension, O passes from the alveoli to the blood, while CO<sub>2</sub> passes from the blood to the alveoli.

It is, however, impossible under certain conditions, and possibly under ordinary conditions, to account for the transmission of all of either the O or the CO<sub>2</sub> by the laws of diffusion. Bohr<sup>1</sup> found in experiments upon dogs that the tension of oxygen in arterial blood is almost invariably higher than the partial pressure of oxygen in the lungs, and in some instances considerably higher. His records as regards CO<sub>2</sub>, while lacking uniformity, are of like import, and indicate that the tension of CO<sub>2</sub> in the blood is lower than the partial pressure of this gas in the lungs. Although Bohr's results have met with much adverse criticism, they have received substantial support in the recent researches of Haldane and Smith<sup>2</sup> on mice, birds, dogs, and other animals. They found that the normal oxygen tension in arterial blood is always higher than in alveolar air, and they were consequently led to conclude

<sup>1</sup> *Skandinavisches Archiv für Physiologie*, 1891, Bd. ii. S. 236.

<sup>2</sup> *Journal of Physiology*, 1897, vol. xxii. p. 231.

that the transmission of O between the alveoli and the blood cannot be satisfactorily explained by mere diffusion. Moreover, about twice as much argon exists in solution in the blood plasma as can be accounted for by physical laws.

Facts of this kind are explicable on the hypothesis that the living tissues are, as contended by Ludwig, Bohr, and others, actively engaged in the process, but our knowledge is as yet too incomplete and contradictory to justify its acceptance. Until, therefore, we are in possession of the results of further research we are justified in the belief that the interchange of O and CO<sub>2</sub> between alveoli and blood is due to physical and chemical factors, diffusion being most important, and that it may be possible that the living tissues take some active part.

**The Forces Concerned in the Interchange of O and CO<sub>2</sub> between the Blood and the Tissues.**—Innumerable facts show that the chief seat of the chemical processes in the body is in the tissues, and that the decompositions are essentially of an oxidizing character whereby CO<sub>2</sub> is formed as one of the most important effete products; consequently the blood as it is carried through the capillaries gives up O and receives CO<sub>2</sub>.

Experiments show that the tissues exert a strong reducing action, and that their avidity for O is so great that they will take it up at extremely low pressures. Moreover, never more than mere traces of O can be obtained from the tissues, because the gas upon its absorption immediately enters into chemical combination.

The tension of CO<sub>2</sub> in the tissues is considerably higher than in blood. Strassburg,<sup>1</sup> in a loop of intestine into which he injected atmospheric air, found that the tension was 58.52 millimeters of Hg, which is considerably greater than in either arterial or venous blood. Thus we find that the tension of O in the tissues is *nil*, owing to the avidity with which substances of the tissues combine with the gas, and its chemical fixation; while that of CO<sub>2</sub> is very high. Comparing the tensions of these two gases in the blood and the tissues, it will be observed that there are present conditions which are highly favorable to the passage of O to the tissues and of CO<sub>2</sub> in the reverse direction:

	O.	CO <sub>2</sub> .
Tensions in arterial blood . . . . .	29.64	21.28
Blood-vessel walls . . . . .	↓	↑
Tensions in tissues . . . . .	0.00	58.25

It is manifest from the above that O should pass from the blood to the tissues, and CO<sub>2</sub> from the tissues to the blood.

The lymph is probably merely a passive medium in this interchange. It contains, according to Hammarsten, only traces of O, from 37.5 to 47.1 volumes per cent. of CO<sub>2</sub>, and from 1.1 to 1.63 volumes per cent. of N. The mean percentage of CO<sub>2</sub> is lower than in serum, but Gaule has shown that the tension is higher. Doubtless the same relations hold good for the plasma and

<sup>1</sup> *Loc. cit.*



the blood, so that, notwithstanding a smaller volume per cent. of  $\text{CO}_2$  in the lymph,  $\text{CO}_2$  passes to the blood because of the higher tension in the lymph.

**Extraction of Gases from the Blood.**—We have found that in the blood both O and  $\text{CO}_2$  exist partly in solution and partly in chemical combination. The portion in solution comes off regularly with a diminution of pressure, but that which is in chemical combination remains so until the pressure is reduced to the level of the tension of dissociation. Since there are several of these combinations, such as O in oxyhæmoglobin and  $\text{CO}_2$  in carbonates, bicarbonates, etc., portions of each of these gases come off at different pressures in accordance with their different tensions in the several chemical combinations. The portions in solution may be removed by the use of an

ordinary air-pump, but those in chemical combination are held so firmly that the more powerful mercurial pump is required. A convenient pump of this kind has been devised by Dr. Geo. T. Kemp, the description of which he gives as follows :

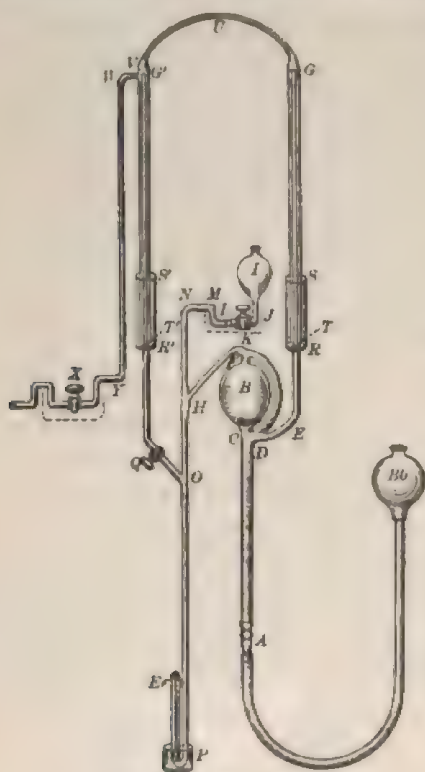


FIG. 74.—Kemp's gas pump.

"To use the pump the reservoir bulb *Bb* (Fig. 74), the bulb *I*, the cylinder *SR* and *S'R'*, and the vessel *P* are filled with mercury. When the bulb *Bb* is raised the mercury rises in the tube *AC* and fills *B*, driving the air out by the path *FHOP*, the stopcock *Q* being closed. When *Bb* is lowered again the mercury flows back from *B* into *Bb*, creating a Torricellian vacuum in *B*. As soon as the mercury has fallen below the joint *D*, this vacuum in *B* becomes connected by the path *DEG* with the tubes *TGUG'T'* and the tube *VWYX*, and thence, when the stopcock is open,

with the vessel to be exhausted. The air in this then diffuses to fill the vacuum in *B*, and becomes rarefied, so that the mercury rises from the cylinders *SR* and *S'R'* in the outer tubes *TG* and *T'G'*. The small inner tubes *RG* and *R'G'* are made so high that even when there is a complete vacuum in the outer tubes *TG* and *T'G'* the mercury will not rise high enough to cover them.

"On raising *Bb* again the mercury rises in *AC*, and as soon as the joint *D* is covered, all the air which has been caught in *B* is forced out by the path *FHOP*. Each time the bulb *Bb* is raised and lowered a certain amount of air is ex-

tracted from the receiver, until finally a vacuum is produced. In a similar way, when the receiver connected with the pump at *Z* contains any gas which we wish to analyze—as, for example, the gases given off by the blood in a vacuum—we put a eudiometer (*Eu*) over the bend of the tube at *P*, which, of course, is always under the mercury, and collect the gases as they are forced out.

“The extraction of the last traces of gas by raising and lowering *Bb* is a very tedious and laborious process, so that the final extraction of the gases can best be accomplished by the Sprengel pump *JKLMNHOP*. The bulb and stopcock *JK* are made separate, as shown in the figure, and are connected with *LMN* by a piece of rubber tubing, the whole being under mercury. This is accomplished by the bend *JKLM*, which is made so as to allow a narrow wooden box filled with the mercury to be slipped up over the bend high enough to cover the stopcock and thus prevent leakage of air. The same arrangement is shown at *X*, and is indicated by a dotted line in each instance. When the stopcock *K* is opened the mercury flows in, drops down the tube *NHOP*, and extracts the gases at *H* in the well-known manner of the Sprengel pump. The large bulb is for rapid exhaustion down to the last few millimeters of pressure, the rest being accomplished more slowly but more perfectly by the Sprengel. In extracting blood-gases the oxygen is given off suddenly and the  $\text{CO}_2$  slowly. The great desideratum is to keep the tension of the gases in the blood-chamber down as near zero as possible—certainly below 20 millimeters of Hg. This is readily done with the large bulb when the *O* is evolved, while the Sprengel is able to remove the  $\text{CO}_2$  as it is given off, thus obviating the continued raising and lowering of the reservoir bulb.”

The gases collected are driven through the tube *P* into a eudiometer previously filled with mercury and inverted. The eudiometer (Fig. 75) is a calibrated tube in which the gases are measured. In the upper part of it are two platinum wires by means of which an electric spark is brought in contact with the gases. Hydrogen is introduced into the eudiometer in definite quantity (more than sufficient to combine with all of the *O* to form  $\text{H}_2\text{O}$ ), and a spark is generated between the ends of the platinum wires, causing the *O* and the *H* to combine. The diminution in volume is now noted, one-third of which diminution is equal to the total volume of *O* obtained from the sample of blood. The quantity of  $\text{CO}_2$  may be estimated by introducing into the eudiometer a piece of moistened fused potassium hydrate, which absorbs the  $\text{CO}_2$ , forming potassium carbonate. The loss in volume is the volume of  $\text{CO}_2$  obtained from the blood. The residual gas consists of *N* and *H*, the latter being the excess not combined with *O*. The total quantity of *H* introduced being known, and also the quantity which combined with *O*, the difference is deducted from the volume *N* and *H*, the remainder being the volume *N*. Accurate analysis necessitates corrections for temperature, for



FIG. 75.—Eudiometer.



tension of aqueous vapor, and for atmospheric pressure, as well as attention to the many details connected with gas-analysis.

**Cutaneous Respiration.**—In frogs the skin is a more important respiratory organ than the lungs, as is illustrated by the fact that asphyxia is more rapidly produced by dipping the animal in oil, and thus preventing the interchange of O and CO<sub>2</sub> through the skin, than by ligature of the trachea; moreover, the investigations of Regnault and Reiset show that in these animals nearly the same quantities of O are absorbed and CO<sub>2</sub> eliminated after the lungs are excised as in the intact animal. In man the reverse is the case, the cutaneous interchange being insignificant as compared with that in the lungs.

The quantity of CO<sub>2</sub> exhaled through the skin during twenty-four hours has been estimated by different observers from 2.23 grams to as much as 32.08 grams. Compared with pulmonary interchange, the ratio of O absorbed is probably about 1 : 100–200, and of CO<sub>2</sub> eliminated, 1 : 200–250.

Cutaneous respiration is, as a rule, subject to the same circumstances that affect the interchange in the lungs, and is accomplished, moreover, in the same way. In some instances, however, it is influenced in the opposite direction; for instance, it is increased by circumstances that hinder pulmonary respiration. Cutaneous respiration is favored by moist skin, and Ronchi found that it was increased by higher external temperature.

**Internal or Tissue-respiration.**—The main object of the respiratory mechanism is to supply the organism with O and to remove the CO<sub>2</sub> resulting from tissue-activity. The organism may be regarded as an aggregation of living cells, each of which during life consumes O and gives off CO<sub>2</sub>. Activity depends essentially upon processes of oxidation; consequently, not only is oxidation necessary for existence, but the quantity of O absorbed must bear a direct relation to the degree of activity. The avidity of the different tissues for O varies greatly, and the differences are doubtless expressions, broadly speaking, of the relative intensities of their respiratory processes. Quinquaud<sup>1</sup> records the following absorption-capacities of 100 grams of each tissue, submitted for three hours to a temperature of 38° :

Muscle . . . . .	23 c.c.	Spleen . . . . .	8 c.c.
Heart . . . . .	21 "	Lungs . . . . .	7.2 "
Brain . . . . .	12 "	Adipose tissue . . . . .	6 "
Liver . . . . .	10 "	Bone . . . . .	5 "
Kidney . . . . .	10 "	Blood . . . . .	0.8 "

The quantity of CO<sub>2</sub> formed in each case was approximately proportional to the quantity of O absorbed. The respiratory value of blood is doubtless too low. The blood is not merely a carrier of O and CO<sub>2</sub> to and from the tissues, but is itself the seat of active disintegrations which involve the consumption of O and the production of CO<sub>2</sub> and other effete matters. Ludwig and his pupils long ago showed that when readily-oxidizable substances, such as lactate of sodium, are mixed with the blood, and the blood is transfused through the lungs or other living tissues, more O is consumed and CO<sub>2</sub> given off than by

<sup>1</sup> *Comptes rendus de la Société de biologie* (9), 1890, 2, pp. 29, 30.

blood free from them. These results have been substantiated by the recent researches of Bohr and Henriquez<sup>1</sup> on dogs, whose experiments have further shown that a considerable portion of O may disappear as a result of processes occurring in the blood during its passage through the lungs, and a large amount of CO<sub>2</sub> be formed as one of the products. Thus they found that considerably more O was absorbed from the lungs than could be pumped from the blood, and that more CO<sub>2</sub> was given to the air in the lungs than was lost by the venous blood. They believe that the tissues deliver to the blood partially-oxidized substances which undergo a final splitting up when the blood reaches the lungs. If this be so, the respiratory capacity of the blood, apart from its capacity as a carrier of O and CO<sub>2</sub> to and from the tissues, must be considerably greater than indicated by Quinquaud's figures.

The chief chemical product of the oxidative decompositions in the blood and tissues is CO<sub>2</sub>; but the quantity of O absorbed is not necessarily related to the amount of CO<sub>2</sub> eliminated; that is, during a given interval the quantity of O may be out of proportion to the elimination of CO<sub>2</sub>, and *vice versa*. Thus, in a muscle during rest, at normal bodily temperature, the consumption of O is greater than the elimination of CO<sub>2</sub>, while during activity the proportion of CO<sub>2</sub> to O increases and may exceed that of O. Rubner's<sup>2</sup> experiments on the resting muscle at various temperatures accentuate the fact that the formation of CO<sub>2</sub> may be independent of the quantity of O absorbed. Thus, at 8.4° the respiratory quotient was 3.28; at 28.2°, 1.01; at 33.8°, 1.18; and at 38.8°, 0.91. The high respiratory quotient at low temperatures is to be explained partly by direct oxidation and partly by intramolecular splitting, which is independent of oxidation. It is probable that during rest O is utilized to some extent in oxidations which are not at once carried to their final stage and in which relatively little CO<sub>2</sub> is formed; hence during activity comparatively little O is required to cause a final disintegration of the now partially broken-down substances, and thus to give rise to a relatively large formation of CO<sub>2</sub>. (See Effects of Muscular Activity on Respiration and Metabolism of Muscle, etc.)

#### C. THE RHYTHM, FREQUENCY, AND DEPTH OF THE RESPIRATORY MOVEMENTS.

**The Rhythm of the Respiratory Movements.**—During normal breathing the respiratory movements follow each other in regular sequence or rhythm. Various instruments have been devised for the study of these movements in man; the form most commonly used is the stethograph or pneumograph of Marey. The respiratory movements are communicated by a system of levers to a tambour, thence through a rubber tube to a second tambour having attached a lever which records upon a moving surface. In animals a tracheal cannula or tube (p. 446) is usually inserted into the trachea, and a tube is led from it to a recording tambour. In case the movements

<sup>1</sup> *Comptes rendus*, 1892, t. 114, pp. 1496-99.

<sup>2</sup> *Du Bois Reymond's Archiv für Physiologie*, 1885, 8, 38-66.



of the ribs are especially to be studied, the stethograph may be employed; if the movements of the diaphragm, a long probe may be inserted through the abdominal walls so that one end rests between the liver and the diaphragm and the other end connects with a recording lever, the abdominal walls serving as a fulcrum. A tracing obtained by one of the above methods shows: (1) That inspiration passes into expiration without an appreciable intervening pause; (2) that inspiration is shorter than expiration; (3) that the curves of inspiration and expiration differ in certain characters. The relative periods of inspiration and expiration vary with age, sex, and other conditions. The inspiratory phase is shorter relatively in women than in men, and in children and the aged than in those of middle life. The length of inspiration as compared to expiration is subject to variations, but these relations are affected chiefly by disease and by other abnormal conditions. After section of the pneumogastric nerves, and in diseased conditions which narrow any part of the air-passages, inspiration is longer than expiration, while in emphysema the expiratory phase is prolonged. The relative periods occupied by inspiration and by expiration in the adult differ according to various observers; at one extreme, the ratio according to Vierordt and Ludwig is 10:19-20, and at the other extreme, according to Ewald, 11:12. A mean ratio is 5:6. Rennebaum found that the expiratory phase is relatively prolonged by an increase in the respiration-rate, the ratio being 9:10 at 13 respirations per minute, and 9:13 at 46 per minute. In the new-born the ratio is 1:2-3. Mosso found that during sleep the inspiratory phase is lengthened one-fourth.

Inspiration is more abrupt than expiration, the lever moving more rapidly during inspiration than during expiration; consequently the curves differ in character. We may volitionally affect the rhythm and the various phases of each respiratory act.

A pause may exist between expiration and inspiration (expiratory pause) when the respirations are abnormally infrequent. In certain diseases an interval may be observed between inspiration and expiration (inspiratory pause). Some observers look upon the nearly horizontal part of the respiratory curve as a record of a pause, but an examination of tracings of normal respirations shows that one phase passes into the other without an appreciable interval.

The respiratory acts while we are awake and quiet are rhythmical, but this rhythm is more or less disturbed during sleep, especially in young children and in the aged. In the latter there may not only be an irregularity in the time-intervals between successive acts, but occasionally long expiratory pauses, giving the movements a peculiar periodical character. In the so-called "Cheyne-Stokes respiration" the rhythm is greatly disturbed. This type is characterized by groups of respiratory movements, each group being separated from the preceding and succeeding ones by more or less marked pauses. The first respiration in each group is very shallow and is followed by movements which successively become deeper and deeper until a maximum is reached; then the successive movements become more and more shallow and finally cease. Each group commonly consists of about 10 to 30 respirations, and is

separated from the preceding and succeeding groups by a variable interval, usually 30 to 45 seconds. This form of respiration is frequently observed in uræmia, after severe hemorrhage, and in certain diseases of the heart and brain. Periodical alterations in the respiratory rhythm may be observed in the last stages of asphyxia, in poisoning by chloral, opium, curare, and digitalis, in certain septic fevers, in certain animals during hybernation, etc. In the human organism, excepting during sleep and in the aged and the very young, such non-rhythmical respirations are always indicative of abnormal conditions.

In warm-blooded animals the movements are generally of a much more rhythmical character than in cold-blooded animals.

**The Frequency and Depth of the Respiratory Movements.**—The respiratory rate is affected by a number of conditions, chiefly species, age, posture, time of day, digestion, activity, internal and external temperature, season, barometric pressure, emotions, the composition of the air, the composition of the blood, the state of the respiratory centres and nerves, etc.

The following figures, compiled from various sources, indicate the wide differences in various *species*, the rates being per minute :

Horse . . . . .	6-10	Pig . . . . .	15-20	Rabbit . . . . .	50-60
Ox . . . . .	10-15	Man . . . . .	16-24	Sparrow . . . . .	90
Sheep . . . . .	12-20	Cat . . . . .	20-30	Guinea-pig . . . . .	100-150
Dog . . . . .	15-25	Pigeon . . . . .	30	Rat . . . . .	100-200

The average rate in man varies according to different investigators, from 11.9 by Vierordt to 19.35 by Ruef. Hutchinson noted 16-24 per minute as a mean of 2000 observations. There is a general, but not an absolute, relationship between the rate and the *size of the body*, as regards both different species and different individuals of the same species: as a rule, the smaller the species the more frequent the respirations; the same holding good for individuals of the same species.

The marked influence of *age* is illustrated by the records of the observations by Quetelet on 300 individuals :

Age.	Rate per Minute.		Mean.
	Maximum.	Minimum.	
New-born . . . . .	70	23	44
1-5 years . . . . .	32	..	26
15-20 " . . . . .	24	16	20
20-25 " . . . . .	24	14	18.7
25-30 " . . . . .	21	15	16
30-50 " . . . . .	23	11	18.1

*Posture* exerts a marked influence, especially in those enfeebled by disease. Guy records, in normal individuals, 13 while lying, 19 while sitting, and 22 while standing.

The *diurnal changes* are in close accord with those of the pulse-rate (p. 121). The rate is less frequent by about one-fourth during the night than during the day, and more frequent after meals, especially after the mid-day meal. Vierordt noted the following variations: 9 A. M., 12.1; 12 M., 11.5; 2 P. M., 13;



7 P.M., 11.1. Guy gives the mean rate in the morning as 17 and in the evening as 18.

The rate increases with an increase in *muscular activity* (p. 121).

Changes in *external* (surrounding) *temperature* have very little influence. Vierordt noted a rate of 12.16 at 8.47° C. and one of 11.57 at 19.4° C., and that an increase of each degree C. increases the period of each respiration about  $\frac{1}{16}$ th, thus lessening the rate. Alterations of *internal temperature* are associated with marked changes, as is well illustrated in the increase in the rate observed in fevers, which increase, in turn, is closely related to the rise in the pulse-rate and the body temperature.

*Season* is not without its influence. In the spring the rate, according to E. Smith, is 32 per cent. greater than at the end of summer.

Ordinary changes in *atmospheric pressure* exert no influence, but under considerable variations the rate rises and falls inversely with the pressure.

The frequency of the respirations may be profoundly affected by our *emotions* and by our *will*. Mental excitement may increase or decrease the rate, and, as is well known, we may greatly modify not only the rate, but also the depth and the rhythm of the movements by volitional effort.

If the *composition of the inspired air* becomes so altered that O falls below 13 volumes per cent., the respirations are increased in frequency and in depth. In the same way, if the blood becomes deficient in O or overcharged with CO<sub>2</sub>, movements of respiration are increased.

Excitation and depression of the *respiratory centres and nerves* through the agency of operations, disease, poisons, etc. effect changes in the respiratory rate.

The *rate and the depth* of the respirations bear generally an inverse relation to each other: the greater the rate the less the depth, and *vice versa*; but the quantity of air respired during a given period does not necessarily bear any direct relation to either the rate or the depth alone, but rather to both.

A general relationship exists between the frequency of the respirations and the pulse-rate. Comparisons of a large number of observations by different investigators give a ratio at twenty-five to thirty-five years, 1:4-4.5; at fifteen to twenty years, 1:3.5; at six weeks, 1:2.5.

#### D. THE VOLUMES OF AIR, O, AND CO<sub>2</sub> RESPIRED.

During quiet respiration there occurs an inflow and outflow of air, designated *tidal air*, equal to about 500 cubic centimeters, or 30 cubic inches. The volume of expired air is a little in excess of inspired air, owing to the expansion caused by the increase of temperature, although the actual volume is less (p. 410). The volume of air respired during each respiration bears generally an inverse relation to the respiration-rate, and is affected by the position of the body; thus, if in the lying posture the volume be 1, when sitting it will be 1.11, and when standing 1.13 (Hutchinson). Besides the term *tidal air*, others are used to express definite volumes associated with the capacity of the lungs under certain circumstances. Thus, Hutchinson distinguishes

*complemental air*, or the volume that can be inspired after the completion of an ordinary inspiration (1500 cubic centimeters); *reserve or supplemental air*, or the volume that can be expelled after an ordinary expiration (1240–1800 cubic centimeters); *residual air*, or the volume remaining in the lungs after the most forcible expiration (1230–1640 cubic centimeters); and *stationary air*, or the volume remaining in the lungs after ordinary expiration, and equal to reserve air plus residual air (2470–3440 cubic centimeters). The volume of residual air is different according to various observers, the estimates ranging within wide limits. Hermann and Berenstein<sup>1</sup> record from observations on sixteen living male subjects a maximum of 1250 cubic centimeters, a minimum of 440 cubic centimeters, and a mean of 796 cubic centimeters.

*Lung-capacity* is the total quantity of air the lungs contain after the most forcible inspiration, and is equal to the vital capacity plus the residual air.

*Bronchial capacity* is the capacity of the trachea and bronchi, and is equal to about 140 cubic centimeters.

*Alveolar capacity* is the volume of air in the smallest air-passages and alveoli, and is greater during inspiration than during expiration, and, of course, is altered in proportion to the depth of these movements. After quiet expiration it is equal to about 2000 to 3000 cubic centimeters; during quiet inspiration it is increased about 500 cubic centimeters, and during forced inspiration about 2000 cubic centimeters; during forced expiration it is diminished about 1500 cubic centimeters. Between the extremes of forced inspiration and forced expiration the volume differs about  $3\frac{1}{2}$  times.

*Vital capacity* is the volume of air that can be expired after the most forcible inspiration. Averages obtained by Vierordt from the results of the observations by various investigators are 3400 cubic centimeters for men and 2500 cubic centimeters for women. Such investigations are conducted by the aid of a spirometer (Fig. 76), which is a calibrated gasometer consisting of a bell-jar submerged in water and counterpoised. Communicating with the interior of the jar is a tube through which the expired air is conducted. The subject makes the deepest possible inspiration and then forcibly expires into the tube; the jar rises in proportion to the volume of air admitted, and the extent of this rise may be read from the scale.



FIG. 76.—Wintrich's modification of Hutchinson's spirometer.

<sup>1</sup> *Archiv für die gesammte Physiologie*, 1891, Bd. 50, S. 363.



Vital capacity is affected by various circumstances, especially age, stature, sex, posture, occupation, and disease. It increases with age, reaching a maximum at about thirty-five years, after which there occurs an annual decrease of about 32 cubic centimeters up to about sixty-five years. In proportion to the length of the body it increases up to twenty-five years and then diminishes. Wintrich has shown that vital capacity for each centimeter of height varies at different ages; thus at eight to ten years it is 9 to 11 cubic centimeters for each centimeter of height, at sixteen to eighteen years 20.65 cubic centimeters, and at fifty years 21 cubic centimeters. Arnold estimates that in the adult for each centimeter of increase or decrease of height beyond a mean standard there is a corresponding rise or fall of 60 cubic centimeters in men and of 40 cubic centimeters in women. It is greater in men than in women of the same height, the ratio being about 10:7.5. Hutchinson found that it was affected by posture, the ratios being as follows: Lying on chest and abdomen, 0.96; lying on back or sitting, 1.11; and standing, 1.13. Wintrich and Arnold both have found that vital capacity is diminished during starvation 100 to 200 cubic centimeters. Physical exercise, such as running and other forms of violent exertion that increase the rate and depth of respiration, tends to increase the vital capacity. Occupation also exerts an influence upon vital capacity, it being proportionately greater in those engaged in active physical work than in those leading a sedentary life. All circumstances which interfere with the full and free expansion of the thoracic cavity diminish vital capacity, as, for instance, tight clothing, visceral tumors, tuberculosis of the lungs, pneumothorax, etc.

**The Volumes of O and CO<sub>2</sub> Respired.**—The quantity of air respired during each respiratory act is about 500 cubic centimeters, or 30 cubic inches; and since the normal respiration-rate in man is, we may say, for the twenty-four hours about 15, the total quantity of air respired per diem may readily be calculated:

Per minute, 500 c.c.  $\times 15 = 7,500$  c.c., or 7.5 liters.

Per hour, 7.5 liters  $\times 60 = 450$  liters.

Per day, 450 liters  $\times 24 = 10,800$  liters, or about 380 cubic feet, which is equal to a volume about 220 centimeters (7½ feet) in height, width, and thickness.

With these figures as standards, and knowing the per cent. composition of inspired and expired air, the volumes of O absorbed and of CO<sub>2</sub> eliminated are easily found. The inspired air loses 4.78 volumes per cent. of O; it is obvious, then, that the quantity absorbed per diem is 4.78 volumes per cent. of 10,800 liters, which is 516 liters, or about 740 grams; likewise, the expired air contains an excess of 4.34 volumes per cent. of CO<sub>2</sub>; the quantity expired per diem is 4.34 volumes per cent. of 10,800 liters, or 470 liters or 925 grams. These figures, while not strictly accurate, are in accord with those obtained by other methods of estimation and by experiments. The amount of O varies from 600 to 1200 grams per diem, and that of CO<sub>2</sub> from 700 to 1400 grams—approximate averages being about 750 grams of O and 875 grams of CO<sub>2</sub>.

The quantities of O and of CO<sub>2</sub> exchanged, although in a general way closely related, are in a measure independent of each other, but, as a rule, an increase or a decrease in one is accompanied by a rise or a fall in the other. The most important conditions affecting the quantities of O absorbed and CO<sub>2</sub> given off are species, body-weight and body-surface, age, sex, constitution, rate and depth of the respirations, the period of the day, digestion, food, internal and external temperature, activity, atmospheric pressure, the composition of the inspired air, and the condition of the nervous system.

Most of the studies have been made solely by determinations of the quantities of CO<sub>2</sub> given off, the results being taken as standards for the relative volumes of O absorbed; but such deductions are of very uncertain value and may be entirely misleading. (See Respiratory Quotient, p. 436.)

Respiratory activity in different *species* in proportion to body-weight is less in cold-blooded than in warm-blooded animals, the difference being due chiefly to the larger supply of O demanded by the more active heat-producing processes in the latter, and in part to the more active character generally of the bodily operations. If we take as a standard for cold-blooded animals the respiratory activity in the frog (which is 0.07 gram of O per kilogram of body-weight per hour), and compare this with the standards for warm-blooded animals, in the latter it will be from 6 to 18 times greater, according to the species. Respiratory activity is higher in proportion to body-weight in birds than in mammals. The following tabular statement of the intensity of the respiratory interchange per kilogram of body-weight per hour, compiled chiefly from the researches of Regnault and Reiset, Zuntz and Lehmann, Bossignault, Herzog, and Grouven, illustrates these differences:

Animal.	O.		CO <sub>2</sub> .		CO <sub>2</sub> . O
	Grams.	C.c.	Grams.	C.c.	
Finch . . . . .	11.835	1837	11.540	5857	0.72
Sparrow . . . . .	9.595	6710	10.492	5334	0.79
Fowl . . . . .	1.189	831	1.271	678	0.82
Frog . . . . .	0.070	49	0.062	37	0.76
Dog . . . . .	1.191	847	1.281	652	0.77
Cat . . . . .	1.001	699	1.082	549	0.80
Ox . . . . .	0.550	382	0.757	383	1.00
Ass . . . . .	0.566	394	0.393	394	1.00
Calf . . . . .	0.481	336	0.571	290	0.86
Horse . . . . .	0.437	303	0.640	323	0.91
Sheep . . . . .	0.499	347	0.599	304	0.88
Rabbit . . . . .	0.920	642	1.158	588	0.90
Man . . . . .	0.434	302	0.507	257	0.85
Pig . . . . .	0.474	331	0.594	302	0.91

As a rule, the smaller the species the greater (relatively, but not absolutely) is the intensity of respiratory activity; for instance, the consumption of O for each kilogram of body-weight is for the horse, 0.437; ass, 0.566; sheep, 0.499; rabbit, 0.92; and for birds, as high as 12.58. For different species of the same class the same variations are observed; thus, Richet records, as the result of investigations on birds, the following figures as the number of



grams of  $\text{CO}_2$  given off per kilogram of body-weight per hour: Goose, 1.49; fowl, 1.66; duck, 2.27; pigeon, 3.36; and finch, 12.58.

In the same species, other things being equal, the respiratory interchange is greater in smaller animals, because in relation to *body-weight* the *body-surface* is greater, causing a greater proportional heat-loss, which in turn necessitates a larger consumption of O for oxidative processes to produce heat, and a consequent increase in the production of  $\text{CO}_2$ . Richet<sup>1</sup> has shown that in the same species the quantity of  $\text{CO}_2$  exhaled (indicating the intensity of the oxidation-processes) is inversely proportional to the body-weight and is directly proportional to the body-surface. The following figures illustrate these important facts:

Mean Body-weight (kilograms).	$\text{CO}_2$ per Kilogram per Hour (grams).	Body-surface (sq. cm.).	$\text{CO}_2$ per 100 sq. cm. (grams).
24	1.026	9206	2.65
11.5	1.380	5656	2.81
6.5	1.624	3040	2.69
3.1	1.964	2341	2.71

Thus, an animal weighing 24 kilograms will give off 1.026 grams of  $\text{CO}_2$  per hour for each kilogram of body-weight, while one weighing 3.1 kilograms will give off 1.964 grams, or nearly twice as much, for equal increments of weight. It will be observed by comparing the quantity of  $\text{CO}_2$  and the body-surface that for each 100 square centimeters of surface the elimination is about the same.

*Age* exercises an important influence. Until full growth respiratory activity is higher than in middle life, and in middle life it is higher than in old age. In children the absolute quantities of O consumed and  $\text{CO}_2$  formed are less than in the adult, but in relation to body-weight they are about twice as much. During middle life respiratory activity is about one-sixth higher than during old age. In the young the quantity of O in relation to  $\text{CO}_2$  is higher than in the adult.

Andral and Gavarret have shown, in investigations relative to *sex*, that after the eighth year males give off from one-third to one-half more  $\text{CO}_2$  than females, the difference being most pronounced at puberty. During pregnancy and after the menopause the relative quantity of  $\text{CO}_2$  rises.

The influence of *constitution* is manifest by a greater intensity of respiratory activity in the robust than in the weak, other conditions being the same.

The *rate and depth of the respiratory movements* do not appreciably affect the volumes of O and  $\text{CO}_2$  interchanged, although the removal of  $\text{CO}_2$  is facilitated by an increase of the volume of air respired, because of the better ventilation of the lungs. An increase in the rate, the depth remaining constant, increases the volume of air respired and the absolute quantity of  $\text{CO}_2$  given off, but the quantity of  $\text{CO}_2$  in relation to the total volume of air is less. If

<sup>1</sup> *Archives de Physiologie normale et pathologique*, t. 22, pp. 17-30.

the rate remain constant and the depth be increased, similar results are obtained.

The quantity of  $\text{CO}_2$  eliminated during slow, deep respirations is larger than during rapid, shallow respirations.

The *diurnal variations* are in accord with the changes in the respiratory rate—rising after we awake, falling during the forenoon, again rising after the mid-day meal, again falling during the afternoon, increasing after the evening meal, and falling to a minimum during the night.

*Sunlight* exercises a marked influence, as is proven by the results obtained by a number of investigators. In frogs the elimination of  $\text{CO}_2$  is increased by sunlight, even after excision of the lungs. Fubini and Benedicenti,<sup>1</sup> in experiments upon hibernating animals, found that the comparative quantities of  $\text{CO}_2$  eliminated under the influence of sunlight and of darkness were as 100:93.48. Fubini and Spallitta<sup>2</sup> have also shown that different colored lights variously affect the output of  $\text{CO}_2$  in different species.

Respiratory activity is affected by the character and quantity of the *food*. The following results, obtained by Pettenkofer and Voit, are very instructive:

	Fasting.	Mixed Diet.	Non-nitrogenous Diet.	Nitrogenous Diet.
O . . . . .	743 grams.	867 grams.	808 grams.	1083 grams.
$\text{CO}_2$ . . . . .	695 "	930 "	839 "	850 "

It will be observed that respiratory activity is lowest during fasting, higher when the diet is non-nitrogenous, still higher when the diet is mixed, and highest when the diet is purely nitrogenous. The respiratory quotient is higher when the diet is rich in carbohydrates (p. 437), while it falls in proportion to the percentage of nitrogenous food. Fasting reduces the quotient considerably, and if coupled with inactivity (hibernation) causes it to fall to a minimum.

During *digestion* the gaseous exchange is increased, according to Loewy,<sup>3</sup> from 7 to 30 per cent. Joylet, Bergonie, and Sigalas<sup>4</sup> obtained the following averages of seven experiments on a man weighing 52 kilograms, the increase of O being about 7 per cent., and of  $\text{CO}_2$  about 6 per cent.:

	O.	$\text{CO}_2$ .
Before food . . . . .	259 c.c.	298.4 c.c.
After food . . . . .	275 "	317 "

The increase of respiratory activity during digestion may be due to the chemical processes involved in the production of the digestive secretions, to the oxidation of the products of digestion after absorption, or to muscular activity of the gastro-intestinal walls. Zuntz and Mering<sup>5</sup> endeavored to

<sup>1</sup> *Moleschott's Untersuch. z. Naturk.*, 1887, Bd. 14, S. 623-629.

<sup>2</sup> *Ibid.*, 1886, Bd. 13, S. 563.

<sup>3</sup> *Archiv für die gesammte Physiologie*, 1888, Bd. 43, S. 515-532.

<sup>4</sup> *Comptes rendus*, 1887, t. 105, pp. 390, 675.

<sup>5</sup> *Archiv für die gesammte Physiologie*, 1883, Bd. 32, S. 173-221.



settle this point by making three series of experiments: in one they injected certain readily oxidizable substances into the blood; in another the substances were injected into the stomach; and in another sulphate of sodium or other purgative was given. When the substances were injected into the blood, Zuntz and Mering found as a general result that the absorption of O was not increased, while the formation of CO<sub>2</sub> was slightly increased; when injected into the stomach, no marked increase in respiratory activity occurred unless the substances were given in large quantities. When, however, in addition to the readily oxidizable substances, a purgative was injected, or when the purgative was given alone, the absorption of O and the elimination of CO<sub>2</sub> were considerably increased. They were therefore led to conclude that the increased respiratory interchange during digestion is due chiefly to the muscular activity of the intestinal walls. Loewy<sup>1</sup> has confirmed this conclusion, and has clearly shown that the increase in respiratory activity is chiefly related to the intensity of peristalsis, the most marked increase being associated with excessive peristaltic activity. There can be no reasonable doubt, however, that a portion of the increase is due both to glandular activity and to the breaking down of the absorbed products of digestion.

The volumes of O absorbed and of CO<sub>2</sub> produced rise with an increase of *body temperature*. This fact has been illustrated by the experiments of Pflüger and Colasanti on guinea-pigs, in which they found that the quantity of O absorbed at a body temperature of 37.1° was 948.17 cubic centimeters; at 38.5°, 1137.3 cubic centimeters; at 39.7°, 1242.6 cubic centimeters, per kilo per hour. Similar results have been obtained by other investigators in experiments both upon the human subject and upon the lower animals under the pathological conditions of fever. A fall of body temperature is accompanied by a decrease in the intensity of respiration, unless the fall is accompanied by muscular excitement, such as shivering. Speck<sup>2</sup> has seen shivering cause the consumption of O to rise from 302 to 496 cubic centimeters, and the exhalation of CO<sub>2</sub> from 287 to 439 cubic centimeters. The primary and fundamental effect of lowering the body temperature is to diminish respiratory activity, but this may be more than compensated for by involuntary or voluntary excitement of the muscles (p. 433; see also Tissue-respiration).

The effects of *external temperature* upon warm- and cold-blooded animals are different: Moleschott found that frogs produced three times more CO<sub>2</sub> at 38.7° than at 6°, while in warm-blooded animals the opposite is the case—that is, three times more CO<sub>2</sub> is formed at the lower temperature. The frog's temperature rises and falls with changes in the temperature of the surroundings, while that of warm-blooded animals remains at a fairly constant standard; hence the respiratory intensity in the frog increases with the rise of external temperature, while in warm-blooded animals it decreases, owing to diminished heat-production. But in warm-blooded animals the alterations in respiratory activity caused by changes of external temperature are not always in inverse relation. Thus, Voit has shown, as a result of studies in man, that the exhalation

<sup>1</sup> *Loc. cit.*<sup>2</sup> *Deutsches Archiv f. klin. Med.*, 1889, Bd. 33, S. 375, 424.

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tion of  $\text{CO}_2$  diminishes with the rise of external temperature from  $4.4^\circ$  until the temperature reaches  $14.3^\circ$ , when it rises slowly. These results have been substantiated by the more recent investigations of Page,<sup>1</sup> who found in experiments on dogs that the discharge of  $\text{CO}_2$  was at a minimum at about  $25^\circ$ ; that below this temperature the quantity increased as the temperature fell; and that above this temperature the discharge increased, and became greatly augmented at temperatures of  $40^\circ$  to  $42^\circ$ . At the latter temperatures the increase may reach  $3\frac{1}{2}$  times the normal, but the *bodily temperature* is also increased. If the elimination of  $\text{CO}_2$  at  $23^\circ$  to  $24^\circ$  be represented by 100 as a standard, at  $13^\circ$  it will be about 128; at  $10^\circ$ , 141; and at  $8^\circ$ , 177. The researches of Speck,<sup>2</sup> of Loewy,<sup>3</sup> of Quinquaud,<sup>4</sup> and of Johansson<sup>5</sup> all show that external cold increases respiratory activity, chiefly or solely by causing involuntary muscular excitement (shivering). If shivering and other forms of muscular activity be absent, the exchange of O and  $\text{CO}_2$  is unaffected or even diminished, but when present the increase of respiratory activity may amount to 100 per cent. notwithstanding a fall of bodily temperature below the normal.

Muscular activity is one of the most important of all the circumstances affecting the quantities of O and  $\text{CO}_2$  exchanged. Involuntary excitement, such as shivering, may of itself double the consumption of O and increase two and a half times the elimination of  $\text{CO}_2$ , but volitional muscular effort may increase the interchange even beyond these limits. Hirn, in investigations on four men, noted during rest an hourly absorption of 30.2 grams of O, and during work 120.9 grams; and Pettenkofer and Voit, in similar studies, found an increase of O from 867 grams during rest to 1006 grams during moderate work, and from 930 grams of  $\text{CO}_2$  to 1137 grams. In experiments on the horse Zuntz and Lehmann<sup>6</sup> obtained the following results, which show to what a marked extent the respiratory interchange may be increased by muscular activity:

	Liters per Minute.		
	O.	$\text{CO}_2$ .	$\frac{\text{CO}_2}{\text{O}}$ .
Resting . . . . .	1.722	1.570	0.92
Walking . . . . .	4.766	4.342	0.90
Trotting . . . . .	8.093	7.516	0.93

Speck<sup>7</sup> has added some interesting facts to our knowledge of the effects of muscular activity on the respiratory interchange. Thus, he found that the increase of O and  $\text{CO}_2$  reaches a maximum before exertion reaches its maximum; that the increase for the same amount of work can be varied by changing the position of the body; that if a given amount of work be divided into two equal parts, the increase of respiratory activity during the first period is greater than during the second; that the greater the increase of  $\text{CO}_2$ , the less,

<sup>1</sup> *Journal of Physiology*, 1879-80, vol. 2, p. 228.

<sup>2</sup> *Loc. cit.*

<sup>3</sup> *Archiv für die gesammte Physiologie*, 1890, Bd. 46, S. 189-224.

<sup>4</sup> *Comptes rendus*, 1887, t. 104, pp. 1542-1544.

<sup>5</sup> *Skandinavisches Archiv für Physiologie*, 1897, Bd. 7, S. 123-177.

<sup>6</sup> *Journal of Physiology*, 1890, vol. 2, p. 396.

<sup>7</sup> *Deutsches Archiv f. klin. Med.*, 1889, Bd. 45, S. 460-528.



proportionately, is the increase of O, so that the respiratory quotient rises more and more, and to such an extent that the CO<sub>2</sub> contains more O than is at the time absorbed; and that the quantity of air respired is so intimately related to the amount of CO<sub>2</sub> given off that he regards the quantity of this gas formed as the regulator, as it were, of the degree of activity of the respiratory movements.

Grüber<sup>1</sup> states that while respiratory activity is proportional to the intensity of muscular activity, "training" diminishes the quantity of CO<sub>2</sub> given off for the same amount of work. Thus, taking 1 as a standard of the amount of CO<sub>2</sub> eliminated during rest, he obtained the following ratios in two series of observations:

	Resting.	Walking.	Climbing hills when not used to it.	Climbing hills when used to it.
First series . . . . .	1	1.89	4.1	3.3
Second series . . . . .	1	1.75	3.05	2.42
Mean . . . . .	1	1.82	3.57	2.86

Training therefore reduces the output about 20 per cent.

The elimination of CO<sub>2</sub> is about one-fifth less during sleep than while awake and quiet; from one-fifth to one-half greater during ordinary exertion; from two to two and a half times greater during violent exercise; and about three times greater during tetanus.

During hibernation the absorption of O falls to  $\frac{1}{4}$  and the elimination of CO<sub>2</sub> to  $\frac{1}{7}$  of the normal for the period of activity (Valentine). Relatively more O is absorbed than CO<sub>2</sub> given off, hence the respiratory quotient falls, reaching as low as 0.50 to 0.75.

A diminution of the *barometric pressure* increases the respiration-rate and the volume of air respired, but both Mosso and Marceet have shown that if allowances be made for the increase of volume of the air at the lower pressure, the actual volume respired is less. Conversely, an increase of pressure lowers the rate and the volume of air respired. Extremes of pressure severely affect the respiratory and other functions (p. 451).

The integrity of the *nervous apparatus* which governs the metabolic processes in the tissues is obviously of fundamental importance. If the efferent nerve-fibres of a muscle be cut, the interchange of O and CO<sub>2</sub> at once sinks, as illustrated by the following results obtained by Zuntz:

	O consumed.	CO <sub>2</sub> given off.
Before section . . . . .	13.2 c.c.	14.4 c.c.
After section . . . . .	10.45 c.c.	10.1 c.c.
After section (less) . . . . .	2.75 c.c.	4.3 c.c.

The consumption of O was therefore lessened about 20 per cent., and the formation of CO<sub>2</sub> about 30 per cent.

After section of the spinal cord in the dorsal region Quinquand<sup>2</sup> obtained

<sup>1</sup> *Zeitschrift f. Biologie*, 1891, Bd. 28, S. 466-491.

<sup>2</sup> *Compt. rend. Soc. Biologie*, 1887, pp. 340-342.

similar results. Before the section the blood in the crural vein contained 9.5 per cent. of O and 60 per cent. of CO<sub>2</sub>; after section it contained 13.5 per cent. of O and 40 per cent. of CO<sub>2</sub>, showing that the consumption of O by the tissues and the formation of CO<sub>2</sub> were considerably lessened. After destruction of the spinal cord respiratory activity falls to a minimum.

The study of the effects of *alterations in the composition of the inspired air* on the absorption of O and the elimination of CO<sub>2</sub> are of great importance. Nitrogen is merely a mechanical diluent of the inspired air, and may be replaced by H or by other inert gas, so that alterations in its percentage do not, *per se*, affect the respiratory phenomena; but changes in the percentages of O and CO<sub>2</sub> may cause marked disturbances both of the respiratory movements and of the gaseous interchange.

When the percentage of O in the inspired air is increased up to 40 volumes per cent., Bert found that there occurred an increase in the quantity absorbed, and both Speck and Fredericq have noted merely a transient increase under similar circumstances; but the results of most experimenters, on the contrary, seem to show quite conclusively that an increase of the per cent. of O above the normal does not affect the quantity absorbed. Lukjanow<sup>1</sup> in a large number of experiments could not detect any increase, and Saint-Martin,<sup>2</sup> in researches on guinea-pigs and rats with an atmosphere containing from 20 to 75 volumes per cent. of O, noted the same result. Even in an atmosphere of pure O animals breathe as though they were respiring normal atmospheric air.

A decrease in the percentage of O is without influence until the proportion falls below 13 volumes per cent. Worm-Müller long ago showed that animals breathe quietly in air containing 14.8 volumes per cent. of O, and that if the proportion fell to 7 volumes per cent., respiration became slow, deep, and difficult; with 4.5 volumes per cent. marked dyspnoea occurred; and when there was but 3 volumes per cent. asphyxia rapidly supervened. The more recent results of Speck<sup>3</sup> not only confirm the main facts of Worm-Müller's observations, but furnish other important data. He has shown that when the atmosphere contains 13 volumes per cent. of O, respiration is quiet and the quantity of O absorbed is but slightly, if at all, diminished, and that even when the proportion falls to 9.65 volumes per cent. breathing is carried on for a long time without inconvenience, the amount of O absorbed, however, being diminished. He shows, moreover, that when the volume of O in the atmosphere falls to 8 per cent. the respiratory movements are deep and are but slightly accelerated, the quantity of O absorbed being very much diminished, and that the animal subjected to such an atmosphere succumbs in a few moments. The quantity of O taken into the lungs falls proportionately with the diminution of O in the inspired air until the reduction reaches 11.26 volumes per cent., but further diminution is compensated for by an increase in the volume of air respired. As the volume per cent. of O in the inspired air

<sup>1</sup> *Zeitschrift f. physiolog. Chemie*, 1883-1884, Bd. 8, S. 313-335.

<sup>2</sup> *Compt. rend.*, 1885, t. 98, pp. 241-243.

<sup>3</sup> *Zeitschrift f. klin. Med.*, 1887, Bd. 12, S. 447-532.



diminishes the relative percentage of O absorbed increases, and this continues until the volume in the inspired air is reduced to 11.26 per cent., 27 per cent. of which is absorbed; below this point no further increase of absorption occurs. As the quantity of O absorbed is reduced the respiratory quotient becomes greater, and may reach as high as 2.218.

When the quantity of O remains at the normal standard and the percentage of CO<sub>2</sub> is much increased, the elimination of the latter is interfered with; and Pflüger has shown that if the percentage of CO<sub>2</sub> be high, dyspnoea ensues, notwithstanding the fact that the blood contains a normal amount of O. When air contains 3 to 4 volumes per cent. of CO<sub>2</sub>, the quantity of CO<sub>2</sub> given off is diminished about one-half. Speck<sup>1</sup> and others have found that the elimination of CO<sub>2</sub> during a given period may be independent of both the percentage of O in the inspired air and the quantity absorbed. An atmosphere containing 10 volumes per cent. of CO<sub>2</sub> is generally believed to be toxic, but Wilson's<sup>2</sup> investigations show that air having even as much as 25 to 30 volumes per cent. may be inhaled with impunity. It is quite probable that in those cases in which small percentages of CO<sub>2</sub> in the inspired air have proven poisonous the gases were contaminated with CO (carbon monoxide). Respiration of an atmosphere of pure CO<sub>2</sub> is followed within two or three minutes by death.

Worm-Müller found that when animals breathe atmospheric air in a *large* closed chamber O disappears and CO<sub>2</sub> accumulates, and death finally occurs, not from a lack of O, but from the increase of CO<sub>2</sub>, as is shown by the fact that at the time of death the quantity of O in the air is sufficient to sustain life. He has shown that animals placed in a closed atmosphere of pure O die from an accumulation of CO<sub>2</sub> in the blood, rabbits succumbing after the retention of a volume of CO<sub>2</sub> equal to one-half the volume of the body, and at a time when the atmosphere contained as much as 50 volumes per cent. of O.

The dyspnoea occurring in an animal confined in an air-tight chamber of *small* size is due to the lack of O, nearly all of the gas being absorbed before the animal dies. If a cold-blooded animal, such as a frog, be similarly exposed, the attraction of hæmoglobin for O is so strong that almost every particle of gas will pass into the blood long before death occurs; and even after the total disappearance of O the elimination of CO<sub>2</sub> is said to continue at the normal rate.

Animals placed in a confined space become accustomed, as it were, to the vitiated air, and survive longer than a fresh animal suddenly thrust into the poisonous atmosphere.

**The Respiratory Quotient.**—The relation between the quantities of O absorbed and CO<sub>2</sub> given off during a given period is expressed as the respiratory quotient. The air during its sojourn in the lungs loses 4.78 volumes per cent. of O and acquires 4.34 volumes per cent. of CO<sub>2</sub>, hence the respiratory quotient is  $\frac{\text{CO}_2, 4.34}{\text{O}, 4.78} = 0.901$ . This quotient is subject to considerable

<sup>1</sup> *Loc. cit.*

<sup>2</sup> *American Journ. Pharmacy*, 1893, p. 561.

variations not only in different species, but in different individuals under varied circumstances. The chief reasons for the differences are:

First, the production of  $\text{CO}_2$  is in a measure independent of the O absorbed, as is proven by the records of various investigators, showing that  $\text{CO}_2$  results both from oxidation-processes and from intramolecular splitting (analogous to fermentation-processes) which may be entirely independent of each other; that the quantity of  $\text{CO}_2$  eliminated may continue under certain circumstances at the normal standard even after the absorption of O has ceased; and that the quantity of O contained in the  $\text{CO}_2$  eliminated during a given time may be larger than the actual quantity absorbed. This may be understood in a general way when we remember that the  $\text{CO}_2$  formed in the body is not the result of an immediate oxidation of the carbon-containing material of the body; on the contrary, some of the O absorbed may be stored, as it were, in the form of complex compounds, which at some later time may undergo disintegration, with the formation of  $\text{CO}_2$ ; or the complex materials introduced as food may undergo a similar disintegration and splitting of the molecules, with the formation of  $\text{CO}_2$  independently of the direct action of the O upon them.

Second, a larger quantity of  $\text{CO}_2$  is formed per unit of oxygen from the disintegration of certain substances than from others, consequently the quotient must be affected by the nature of the substances broken down. Thus, in the formation of  $\text{CO}_2$  from carbohydrates all of the O consumed in the disintegration of the molecules is used in forming  $\text{CO}_2$ , the H already having sufficient O to satisfy it; but in the case of fats and proteids a portion of the O is utilized in the oxidation of H to form  $\text{H}_2\text{O}$ . 6 molecules of O will oxidize 1 molecule of grape-sugar ( $\text{C}_6\text{H}_{12}\text{O}_6$ ) into  $6\text{CO}_2 + 6\text{H}_2\text{O}$ ; hence the quotient is  $\frac{6\text{CO}_2}{6\text{O}_2} = 1$ . In regard to fat, if we take olein,  $\text{C}_3\text{H}_5(\text{C}_{18}\text{H}_{33}\text{O}_2)_3$ , as an example, 80 molecules of O are required to reduce each molecule of the fat to 57 molecules of  $\text{CO}_2$  and 52 molecules of  $\text{H}_2\text{O}$ ; hence the quotient is  $\frac{57\text{CO}_2}{80\text{O}_2} = 0.712$ . In the disintegration of proteid only a part of the C is oxidized into  $\text{CO}_2$ , the remainder being eliminated as a constituent of various complex effete bodies; but it is estimated that the quotient for proteids (albumin) is from 0.75 to 0.81, depending upon the completeness of disintegration.

The respiratory quotient varies with species, food, age, the time of day, internal and external temperature, muscular activity, the composition of the inspired air, etc.

In regard to *species*, the quotient is higher in warm-blooded (0.70 to 1.00) than in cold-blooded animals (0.65 to 0.75); in herbivora (0.90 to 1.00) than in carnivora (0.75 to 0.80); and in omnivora (0.80 to 0.90) than in carnivora, but lower than in herbivora. These differences are due essentially to *diet*, herbivora feeding largely upon carbohydrates, omnivora using carbohydrates to a less extent, and carnivora practically not at all. These observations are substantiated by the fact that during fasting, when the animal is feeding upon its own tissues, the respiratory quotient in all species is the same (0.7 to 0.75).



The quotient is lowered by an animal diet and increased by a vegetable diet, the ratio approximating unity if the diet be sufficiently rich in carbohydrates. Hanriot and Richet<sup>1</sup> in observations on man noted that before feeding the quotient was 0.84 to 0.89; when meat or fat was given the consumption of O was increased, but there was no increase in CO<sub>2</sub>, and the quotient fell to 0.76; when given potatoes it was 0.93; and when the diet was of glucose it reached 1.03. During fasting the quotient falls rapidly. The experiments of Zuntz and Lehmann<sup>2</sup> show that in dogs it falls as low as 0.65 to 0.68 on the second day of fasting, and that on the resumption of food it rises to 0.73 to 0.81.

The influence of *age* is manifest in the fact that in children the quotient is lower than in the adult, more O being absorbed in proportion to the CO<sub>2</sub> given off than after full growth has been reached.

The quotient undergoes a *diurnal variation*. The day-time is more favorable than the night for the discharge of CO<sub>2</sub>, as well as for the absorption of O, owing mainly to greater muscular activity during the day, but the CO<sub>2</sub> is more affected than the O; hence the respiratory quotient is higher during the day. In the recent experiments by Saint-Martin<sup>3</sup> on birds, the mean quotient during the day was 0.83 and during the night 0.72; the ratio for CO<sub>2</sub> for the day and night was 1 : 0.78, and for O 1 : 0.9. During the night the elimination of CO<sub>2</sub> was diminished about 20 per cent., while the absorption of O fell only about 10 per cent.

The quotient is increased by a rise of *external temperature*. Thus, Pflüger and Finkler found in guinea-pigs that the quotient was 0.83 at 36.4° and 0.94 at 26.21°. When the *bodily temperature* is increased, as in fever, the respiratory quotient remains practically unaltered. When the temperature falls below the normal the respiratory quotient increases.

*Muscular activity* is also an important factor. During rest the consumption of O by muscles is greater than the production of CO<sub>2</sub>, while during contraction the difference becomes less and less in proportion to the degree of activity, until finally more CO<sub>2</sub> may be given off than there is O consumed. Sezelkow found in experiments on muscles of rabbits at rest and in tetanus that the respiratory quotient was decidedly increased. A mean of six experiments gives as the quotient during rest 0.543 and during tetanus 0.933; in one-half of the experiments it went above 1, and in one instance to 1.13.

During sleep the output of CO<sub>2</sub> is diminished more than the consumption of O (p. 434), so that the respiratory quotient is less than when awake and quiet.

During hibernation the quotient falls to a minimum—in the marmot as low as 0.49. This is due chiefly to the more decided falling off in the quantity of CO<sub>2</sub>, the CO<sub>2</sub> being reduced to  $\frac{1}{5}$ , and the O to only  $\frac{1}{11}$ ; the animal, however, is not only in a state of muscular quiet, but fasting, which, it will be remembered, is an important factor in lowering the quotient.

<sup>1</sup> *Compt. rend.*, 1888, t. 106, pp. 496-498.

<sup>2</sup> *Berliner klin. Woch.*, 1887, s. 428.

<sup>3</sup> *Compt. rend.*, 1887, t. 106, pp. 1124-1128.

When the *percentage of O in the inspired air* falls so low as to cause marked dyspnoea, the respiratory quotient rapidly rises. This is owing on the one hand to the diminished quantity of O absorbed, and on the other hand to the increased production of  $\text{CO}_2$  as a consequence of excessive activity of the muscles of respiration. Speck (p. 435) found that when the proportion of O was very low the quotient rose as high as 2.258.

#### E. PRINCIPLES OF VENTILATION.

Breathing within a confined space, as in a small unventilated room or in a large room in which a considerable number of persons are assembled, causes a gradual diminution in the quantity of O and an accumulation of  $\text{CO}_2$ , moisture, and organic matter. In regard to O, even in the worst ventilated rooms the atmosphere seldom contains as little as 15 volumes per cent., which is sufficient to permit of undisturbed respiration. When the proportion of  $\text{CO}_2$  exceeds 0.07 volume per cent. the air becomes disagreeable, close, and stuffy—offensive characters which are due neither to the increase of  $\text{CO}_2$  nor to a deficiency of O, but to the presence of odorous principles given off chiefly by the body and clothing. Air from which this organic exhalation is absent may contain considerably more  $\text{CO}_2$  without causing any unpleasant effects. In well-ventilated rooms the proportion of  $\text{CO}_2$  does not exceed 0.05 to 0.07 volume per cent.; in badly-ventilated rooms it may reach 0.25 to 0.30 volume per cent.; while when a large number of individuals are crowded together, as in lecture-rooms, it may be as high as 0.70 to 0.80 volume per cent. This vitiation is further increased by the burning of gas or oil, 150 liters of ordinary coal-gas (enough to supply a large burner for about an hour) consuming all the O in 1200 liters of air, or as much O as is required by the average individual in eight hours, besides loading the air with various deleterious products of combustion.

While the accumulation of  $\text{CO}_2$  even in the worst ventilated rooms is not in itself pernicious, its percentage is a practical working index of the degree of vitiation. It has long been recognized that the atmosphere of crowded, badly-ventilated rooms gives rise to discomfort, and by some the expired air has been erroneously asserted to be toxic. Thus Brown-Séquard and d'Arsonval condensed the moisture of the expired air and found that from 20 to 40 cubic centimeters would kill a guinea-pig; but their results have been contradicted positively by Dastré and Loye, Lehmann, Geyer, and others. The vitiation of the air of badly-ventilated rooms cannot be said to be due to any particular poison, but to an accumulation of odorous principles arising from uncleanly bodies, clothes, and surroundings, and also to an accumulation of  $\text{CO}_2$ , and to a deficiency of O in extreme instances.

The quantity of fresh air required during a given period depends upon the size of the individual, the degree of activity, and the size of the air-space. Assuming that an individual eliminates 900 grams, or 458 liters, of  $\text{CO}_2$  per diem, and that the percentage of  $\text{CO}_2$  is to be kept at a standard not exceeding



0.07 volume per cent., there would be required at least 1,440,000 liters of fresh air during twenty-four hours, or about 60,000 liters (2000 cubic feet) per hour. All circumstances, such as muscular activity, which increase the output of  $\text{CO}_2$ , augment the demand for fresh air. When confined in rooms, every person should have an air-space equal to about 28,000 liters, or 1000 cubic feet, the floor-space should not be less than  $\frac{1}{6}$  of the cubic capacity of the room, and the air should be renewed as often as twice an hour. In lecture-rooms, school-rooms, etc. the air-space per individual is usually very small, so that the renewal must be more frequent and in proportion to the limitation of space per individual.

Ventilation is accomplished by natural and artificial means. The forces of the wind, the differences in temperature within and without the building, the natural diffusion of gases owing to variations in composition, etc., all cause more or less circulation. Artificial ventilation is effected by the use of proper appliances for the forced introduction of air into and expulsion from apartments.

#### F. THE EFFECTS OF THE RESPIRATION OF VARIOUS GASES.

The respiration of pure O takes place without disturbance of the respiratory processes. Lorrain Smith<sup>1</sup> has shown that O at the tension of the atmosphere stimulates the lung-cells to active absorption, at a higher tension acts as an irritant, or pathological stimulant, and produces inflammation. Dyspnoea is developed when the inspired air contains less than 13 volumes per cent. (p. 435). Respiration of pure  $\text{CO}_2$  (p. 436) is fatal within two or three minutes, but an atmosphere containing as much as 25 to 30 per cent. may be respired for a few minutes without ill effect (p. 436). Nitrogen, hydrogen, and carburetted hydrogen ( $\text{CH}_4$ ) may be inhaled with impunity if they contain not less than 13 volumes per cent. of O. The respiration of nitrous oxide or of air containing much ozone rapidly produces anaesthesia, unconsciousness, and death. Carbon monoxide (CO) and cyanogen are decidedly toxic, combining with hemoglobin and displacing oxygen. Sulphuretted hydrogen, phosphoretted hydrogen, arseniuretted hydrogen, and antimoniu-retted hydrogen are all poisonous and are all destructive to hemoglobin. An atmosphere containing 0.4 volume per cent. of sulphuretted hydrogen is said to be toxic. Air containing 2 volumes per cent. of CO (carbon monoxide) is quickly fatal. Certain gases and vapors—as, for instance, ammonia, chlorine, bromine, ozone, etc.—produce serious irritation of the respiratory passages, and may in this way cause death.

#### G. EFFECTS OF THE GASEOUS COMPOSITION OF THE BLOOD ON THE RESPIRATORY MOVEMENTS.

Certain terms are employed to express peculiarities in the respiratory phenomena: *Eupnoea* is normal, quiet, and easy breathing. *Apnoea* is a suspension of the respiratory movements. *Hyperpnoea* is a condition of increased

<sup>1</sup> *Journal of Physiology*, 1899, vol. 24, p. 19.

respiratory activity. *Polypnœa*, *thermopolypnœa*, and *heat-dyspnœa* are forms of hyperpnœa due to heating the blood or the skin. *Dyspnœa* is distinguished by deep and labored breathing; the respiratory rate is usually less than the normal, but in some forms it may be higher. *Asphyxia* (suffocation) is characterized by convulsive respirations which are followed in the final stage by infrequent, feeble, and shallow respirations.

*Eupnœa* is the condition of respiration observed during bodily and mental quiet, the quantities of O and CO<sub>2</sub> in the blood being within the normal mean limits.

*Apnœa* may be produced by rapidly repeated respirations of atmospheric air, under which circumstances the respiratory movements may be arrested for a period varying from a few seconds to a minute or more. This condition is produced most easily upon animals which have been tracheotomized and connected with an artificial respiration apparatus. If under these conditions the lungs are repeatedly inflated with sufficient frequency, and the blasts are then suspended, the animal will lie quietly for a certain period in a condition of apnœa. The respirations after a time begin, usually with very feeble movements which quickly increase in strength and depth to the normal type. The ultimate cause of apnœa is still a mooted question, and the heretofore prevalent belief that it is due to hyperoxygenation of the blood is almost entirely discarded. The connection between the quantity of O in the blood and apnœa is, however, suggested by several facts: thus, apnœa is more marked after the respiration of pure O than after that of atmospheric air, and less marked if the air is deficient in O; moreover, Ewald states that the arterial blood of apnœic animals is saturated with O. These facts naturally lead to the inference that the blood is surcharged with O, and that the respiratory movements are arrested until the excess of O is consumed or until sufficient CO<sub>2</sub> accumulates in the blood to excite respiratory movements. But Head<sup>1</sup> has shown that apnœa can be caused by the inflation of the lungs with pure hydrogen as well as by inflation with air or with pure O, although the apnœic pause after the cessation of the inflations is not so long or may be absent altogether; while Ewald's assertion as to the saturation of the blood with O is contradicted by Hoppe-Seyler, Gad, and others. The fact that the apnœic pause exists for a longer period when O is respired lends confirmation to Gad's theory that it is due in part to the large amount of O carried into and stored up, as it were, in the alveoli—an amount sufficient to supply the blood for a certain period and thus to dispense with respiratory movements. Gad found that even when apnœa follows the inflation of the lungs with air, the air in the lungs contains enough O to supply the blood during the period occupied by the blood in making a complete circuit of the system. The fact, however, that apnœa can be caused by the inflation of the lungs by an indifferent gas such as hydrogen, by which every particle of O may be driven from the lungs, certainly shows that there exists some important factor apart from the O; and this assumption receives support in the observation that after section of the pneumo-

<sup>1</sup> *Journal of Physiology*, 1889, vol. 10, pp. 1, 279.



gastric nerves (the channels for the conveyance of sensory impulses from the lungs to the respiratory centre) it is very difficult to cause apnoea by inflation of the lungs with air, while if pure hydrogen is used violent dyspnoea results. It seems, then, that apnoea cannot be produced after division of the vagi unless there be an accumulation of O in the lungs. These facts suggest that the frequent forced inflations of the lungs excite the pulmonic peripheries of the pneumogastric nerves, thus generating impulses which inhibit the inspiratory discharges from the respiratory centre. This view receives further support in several facts: first, that the same number of inflations, whether of pure O, of air, or of H, causes apnoea, the only difference being the length of the apnoeic pause after the cessation of artificial respiration, which pause lasts for the longest period when O is used, and for the shortest period, or not at all, when H is employed; second, that apnoea cannot be caused by inflation of the lungs with H if the pneumogastric nerves be previously divided; third, that the arrest of respiration which occurs during swallowing ("deglutition-apnoea") is due to an inhibition of the respiratory centre by impulses generated in the terminations of the glosso-pharyngeal nerves (p. 462). It therefore seems evident that apnoea may be due to either gaseous or mechanical factors, or to both, the former being effective, not because of the blood being saturated with O, but because of the increased amount of O in the alveoli—a quantity sufficient for a time to aerate the blood; while the mechanical factors give rise to inhibitory impulses which suspend for a longer or shorter period the rhythmical inspiratory discharges from the respiratory centre, doubtless by depressing the irritability of this centre (p. 455). From the experiment quoted it seems that the first of these factors may alone be sufficient to cause apnoea, but that apnoea is more easily produced, and lasts longer, when both factors act together, as is usually the case.

The form of *hyperpnoea* due to *muscular activity* is owing to the action upon the respiratory centre of certain substances which are formed in the muscles during contraction and are given to the blood. Muscular activity, as is well known, is accompanied by an increase in the rate and depth of the respiratory movements, and when the exercise is violent more or less marked dyspnoea may occur. Some physiologists have been led to the belief that the respiratory centre is connected directly or indirectly with the muscles by means of afferent nerve-fibres which convey impulses to the centre and thus excite it to activity; while others have regarded a diminution of O and an increase of CO<sub>2</sub> in the blood as the cause, the active muscles rapidly consuming the O in the blood and giving off CO<sub>2</sub> in great abundance. But Mathieu and Urbain, and Geppert and Zuntz,<sup>1</sup> have found that the volumes per cent. in the blood of O may be increased, and the volume per cent. of CO<sub>2</sub> decreased, during muscular activity. It is probable that the hyperpnoea is due to products of muscular activity which are given to the blood and which act as powerful excitants to the respiratory centre. The precise nature of the bodies is unknown, but it is probable that they are of an acid character, for

<sup>1</sup> *Archiv für die gesammte Physiologie*, 1888, Bd. 42, S. 189.

Lehmann<sup>1</sup> found that there was a distinct lessening of the alkalinity of the blood after muscular exercise. It is likely that the bodies are broken up in the system, because the results of Loewy's<sup>2</sup> investigations indicate that they are not removed by the kidneys.

*Polypnoea, thermopolypnoea, and heat-dyspnoea* are due to a direct excitation of the respiratory centres through an increase of the temperature of the blood, or reflexly by excitation of the cutaneous nerves by external heat. This condition may be produced, as was done by Goldstein, by exposing the carotids and placing them in warm tubes, thus heating the blood; or, as was done by Richet and others, by subjecting the body to high external heat. Richet in employing this latter method found that dogs so exposed may have a respiratory rate as high as 400 per minute. Ott records marked polypnoea as a result of direct irritation of the tuber cinereum. This form of hyperpnoea is entirely independent of the gaseous composition of the blood; moreover, an animal in heat-dyspnoea cannot be rendered apnoeic, even though the blood be so thoroughly oxygenated that the venous blood is of a bright arterial hue.

*Dyspnoea* is generally characterized by slow, deep, and labored respiratory movements, although in some instances the rate may be increased. Several distinct forms are observed: "O-dyspnoea," due to a deficiency of O; "CO<sub>2</sub>-dyspnoea," due to an excess of CO<sub>2</sub> in the blood; and *cardiac* and *hemorrhagic* dyspnoeas, belonging to the O category.

Dyspnoeas due to the gaseous composition of the blood may be caused either by a deficiency of O or by an excess of CO<sub>2</sub>, but are generally due to both. Dyspnoea from a deficit of O is observed when an animal is placed within a small closed chamber, or when an indifferent gas, such as pure hydrogen or nitrogen, is respired. Under the latter circumstances dyspnoea occurs even though the quantity of CO<sub>2</sub> in the blood be below the normal. If, on the contrary, the animal be compelled to breathe an atmosphere containing 10 volumes per cent. of CO<sub>2</sub>, dyspnoea occurs, notwithstanding an abundance of O (p. 436) both in the air and in the blood; indeed, the quantity of O in the blood may be above the normal. Fredericq<sup>3</sup> in ingenious experiments has directly demonstrated the influence of the quantity of CO<sub>2</sub> in the blood upon the respiratory movements. He took two rabbits or dogs, A and B, ligated the vertebral arteries in each, exposed the carotids, and ligated one in each animal. The other carotid in each was cut, and the peripheral end of the vessel of one was connected by means of a cannula with the central end of the vessel of the other, so that the blood of animal A supplied the head (respiratory centre) of animal B, and *vice versa*. When the trachea of animal A was ligated or compressed the animal B showed signs of dyspnoea, because its respiratory centre was now supplied with the venous blood from A. On the contrary, animal A exhibited quiet respirations, almost apnoeic, because its centre received the thoroughly arterialized blood from B, in which the respiratory movements were augmented. In a second series of experiments blood was transfused through

<sup>1</sup> *Archiv für die gesammte Physiologie*, 1888, Bd. 42, S. 284.

<sup>2</sup> *Ibid.*, S. 281

<sup>3</sup> *Bull. Acad. roy. Méd. Belgique*, t. 13, pp. 417-421.



the head: when the blood was laden with  $\text{CO}_2$  marked dyspnoea resulted; when arterial blood was transfused the normal respirations were restored.

While dyspnoea may be caused by the respiration of an atmosphere either deficient in O ("O-dyspnoea") or containing an excess of  $\text{CO}_2$  (" $\text{CO}_2$ -dyspnoea"), the phenomena in the two cases are in certain respects different: When an animal breathes pure N, thus causing O-dyspnoea, the dyspnoea is characterized especially by frequent respiratory movements with vigorous inspirations, whereas if the atmosphere be rich in O and contain an excess of  $\text{CO}_2$  the respirations are especially marked by a slower rate and by the depth and vigor of the expirations; O-dyspnoea continues for a long time before death ensues, and is more severe; in O-dyspnoea the absorption of O is diminished, but the excretion of  $\text{CO}_2$  is practically unaffected; in O-dyspnoea the attendant rise of blood-pressure (p. 447) is more marked and lasting; in O-dyspnoea death is preceded by violent motor disturbances which are absent in  $\text{CO}_2$ -dyspnoea. Blood poor in O (O-dyspnoea) affects chiefly the inspiratory portion of the respiratory centre (p. 457), while blood rich in  $\text{CO}_2$  ( $\text{CO}_2$ -dyspnoea) affects chiefly the expiratory portion; hence in the former the dyspnoea is manifest especially in an increase in the frequency of the respirations (hyperpnoea) and in the vigor of the inspirations, while in the latter it is manifest in a lessened rate, strong expirations, and expiratory pauses.

The marked increase in the depth of the respiratory movements in  $\text{CO}_2$ -dyspnoea is not solely due to the direct action of  $\text{CO}_2$  upon the respiratory centre, for Gad and Zagari<sup>1</sup> have shown that  $\text{CO}_2$  in abundance in inspired air acts upon the terminations of the sensory nerves of the larger bronchi and thus reflexly excites the respiratory centre. In a research on dogs these observers opened the trachea and passed glass tubes through the trachea and the larger bronchi to the smaller bronchi. Before the tubes were inserted the inhalation of  $\text{CO}_2$  caused a considerable deepening of the respiratory movements, but after the insertion of the tubes, by means of which the gas was carried directly to the smaller bronchi, the characteristic action of the  $\text{CO}_2$  was no longer observed. From the results of these experiments we may conclude that the marked increase in the depth of the respiratory movements in  $\text{CO}_2$ -dyspnoea is due in part to the irritation of the sensory nerve-fibres of the mucous membrane of the larger bronchi.

*Cardiac* and *hemorrhagic* dyspnoeas are chiefly due to the deficiency in the supply of O—the former, to the poor supply of blood due to the enfeebled action of the heart; and the latter, both to this and to the reduced quantity of blood (hemoglobin). All circumstances which enfeeble the circulation or lessen the quantity of hemoglobin therefore tend to cause dyspnoea; hence individuals with heart troubles or weakened by disease or with certain forms of anæmia are apt to suffer from dyspnoea upon the least exertion.

All circumstances which interfere with the interchange of O and the elimination of  $\text{CO}_2$  in the lungs are favorable to the production of dyspnoea,

<sup>1</sup> Du Bois-Reymond's *Archiv für Physiologie*, 1890, S. 588.

as in pneumonia, pulmonary tuberculosis, growths of the larynx, abdominal tumors, etc., especially so upon exertion.

*Asphyxia* is literally a state of pulselessness, but the term is now used to express a series of phenomena caused by the deprivation of air, as by placing an animal in a closed chamber of moderate size. These phenomena may be divided into three stages: the first is one of hyperpnœa; the second, of developing dyspnœa, and finally of convulsions; and the third, of collapse. During the first stage the inspiratory portion of the respiratory centre especially is excited, the respirations being increased in frequency and depth. During the second stage the excitation of the expiratory portion of the respiratory centre is more intense than that of the inspiratory portion, so that the respirations become slow and deep, prolonged and convulsive, and the movements of inspiration are feeble and in striking contrast to the violent spasmodic expiratory efforts. During the third stage the dyspnœa is followed by general exhaustion; the respirations are shallow and occur at longer and longer intervals, the pupils become dilated, the motor reflexes disappear, consciousness is lost, the inspiratory muscles contract spasmodically with each inspiratory act, convulsive twitches are observed in the muscles of the extremities and elsewhere, gasping and snapping respiratory movements may be present, the legs are rigidly outstretched and the head and body are arched backward, feces and urine are usually voided, respiratory movements cease, and finally the heart stops beating. During these stages the circulation has undergone considerable disturbances. During the first and second stages the blood has been robbed of nearly all its O, the gums, lips, and skin become cyanosed, and, owing to the venous condition of the blood, the cardio-inhibitory centre has been decidedly excited, so that the heart's contractions are rendered less frequent; the vaso-constrictor centre for the same reason has also been excited, causing a constriction of the capillaries and an increase of blood-pressure. During the third stage these centres are depressed and finally are paralyzed.

If asphyxia be caused by ligating the trachea, the whole series of events covers a period of four to five minutes, the first stage lasting for about one minute, the second a little longer, and the third from two to three minutes. If asphyxia be produced gradually, as by placing an animal within a relatively large confined air-space, death may occur without the appearance of any motor disturbances (p. 436).

The heart usually continues beating feebly for several minutes after the cessation of respiration, so that by means of artificial respiration it is possible to restore the respiratory movements and other suspended functions. After death the blood is very dark, almost black. The arteries are almost if not entirely empty, while the veins and lungs are engorged.

Death from drowning occurs generally from the failure of respiration, occasionally from a cessation of the heart's contractions. It is more difficult to revive an animal asphyxiated in this way than one which, out of water, has simply been deprived of air for the same length of time. Dogs submerged for one and a half minutes can rarely be revived, but recovery can usually be



accomplished after deprivation of air, out of water, for a period four to five times longer. After a person has been submerged for five minutes it is extremely difficult to effect resuscitation.

#### H. ARTIFICIAL RESPIRATION.

Effective methods for maintaining ventilation of the lungs are important alike to the experimenter and to the clinician. In the laboratory the usual method is to expose the trachea, insert a cannula (Fig. 77), and then periodically force air into the lungs by means of a pair of bellows or a pump. Some of the forms of apparatus are very simple, while others are complicated. An ordinary pair of bellows does very well for short experiments, but for longer



FIG. 77.—Cannulae for dogs (a) and for cats and rabbits (b).

study, especially when it is necessary that the supply of air should be uniform, the bellows are operated by power. Some of these instruments are so constructed that air is alternately forced into and withdrawn from the lungs.

Periodical inflation of the lungs is termed *positive* ventilation; the periodical withdrawal of air from the lungs by suction is *negative* ventilation; and

alternate inflation and suction is *compound* ventilation.

In practising artificial respiration we should imitate the normal rate and depth of the respiratory movements. Long-continued positive ventilation causes cerebral anæmia, a fall of blood-pressure, and decrease of bodily temperature.

In human beings it is not practicable, except under extraordinary circumstances, to inflate the lungs by the above methods, so that we are dependent upon such means as will enable us to expand and contract the thoracic cavity without resorting to the knife. One method is to place the individual on his back, the operator taking a position on his knees at the head, facing the feet. The lower ribs are grasped by both hands and the lower antero-lateral portions of the thorax are elevated, thus increasing the thoracic capacity, with a consequent drawing of air into the lungs; the ribs and the abdominal muscles are then pressed upon in imitation of expiration. These alternate movements are kept up as long as necessary.

The following is Sylvester's method: "Place the patient on the back, on a flat surface inclined a little upward from the feet; raise and support the head and shoulders on a small firm cushion or folded article of dress placed under the shoulder-blades. Draw forward the patient's tongue, and keep it projecting beyond the lips; an elastic band over the tongue and under the chin will answer this purpose, or a piece of string or tape may be tied around them, or by raising the lower jaw the teeth may be made to retain the tongue in that position. Remove all tight clothing from about the neck and chest, especially the braces" . . . . "To imitate the movements of breathing: Standing at the

patient's head, grasp the arms just above the elbows, and draw the arms gently and steadily upward above the head, and keep them stretched upward for two seconds. By this means air is drawn into the lungs. Then turn down the patient's arms, and press them gently and firmly for two seconds against the sides of the chest. By this means air is pressed out of the lungs. Repeat these measures alternately, deliberately, and perseveringly about fifteen times in a minute, until a spontaneous effort to respire is perceived, immediately upon which cease to imitate the movements of breathing, and proceed to induce circulation and warmth."

A new and effective method has been reported by Calliano: The patient is placed in Sylvester's position; the arms are drawn up above and behind the head, and the wrists tied. This causes the thorax to be expanded. Respiration is accomplished by pressing concentrically with the open hands upon the sides of the thorax and the epigastric region about twenty times a minute. This method is even more effective if in addition the jaw be wedged open, and short, sharp tractions of the tongue be practised immediately preceding each pressure upon the thorax. These operations should be continued for at least one and a half hours, if necessary, and aided by friction, external heat, etc. The periodical traction of the tongue acts as a strong excitant to the respiratory centre.

#### I. THE EFFECTS OF THE RESPIRATORY MOVEMENTS ON THE CIRCULATION.

The respiratory movements are accompanied by marked changes in the circulation. If a tracing be made of the blood-pressure and the pulse (Fig. 78), and at the same time the inspiratory and expiratory movements be noted, it

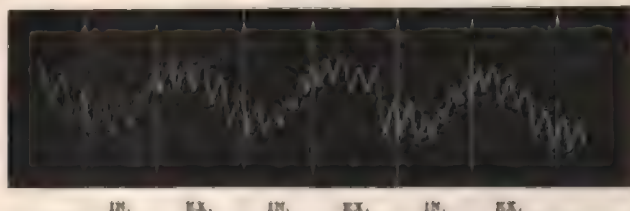


FIG. 78.—Blood-pressure and pulse tracing showing the changes during inspiration (IN.) and expiration (EX.).

will be seen that the blood-pressure begins to rise shortly after the onset of inspiration, commonly after a period occupied by one to three heart-beats, and reaches a maximum after the lapse of a similar brief interval after the beginning of expiration, when it begins to fall, reaching a minimum after the beginning of the next inspiration. During inspiration the pulse-rate is more frequent than during expiration and the character of the pulse-curve is somewhat different.

**The Effects on Blood-pressure.**—The changes in blood-pressure are mechanical effects due to the actions of the respiratory movements. When it



is remembered that the lungs and the heart with their great blood-vessels are placed within an air-tight cavity, that the lungs become inflated through the aspiratory action of the muscles of inspiration, and that during inspiration intrathoracic negative pressure is increased, it is easy to understand how the action which causes inflation of the lungs must affect in like manner such hollow elastic structures as the heart and the great blood-vessels, and thus influence the circulation. It is obvious, however, that this influence must make itself felt to a more marked degree upon the vessels than upon the heart, and upon the flaccid walls of the veins than upon the comparatively rigid walls of the arteries. Moreover, the effects upon the flow of blood through the vessels entering and leaving the thoracic cavity must be different: the inflow through the veins must be favored, and the outflow through the arteries hindered; but it is upon the flaccid veins chiefly that the mechanical influences of inspiration are exerted. If the thoracic cavity be freely opened, movements of inspiration no longer cause an expansion of the lungs, nor is there a tendency to distend the heart and the large blood-vessels; if, however, in an intact animal the outlet of the thorax be restricted, as by pressure upon the trachea, the force of the inspiratory movement would make itself felt chiefly upon the heart and the vessels, and it is under such circumstances that the maximal influences of inspiration upon the circulation are observed. The lungs on the one hand and the heart and its large vessels on the other may be regarded as two sacs placed within a closed expansible cavity, the former having an outlet communicating with the external air, and the latter having inlets and outlets communicating with the extrathoracic blood-vessels, both being dilated when the thorax expands and constricted when it contracts. Moreover, the blood-vessels in the lungs may be compared to a system of delicate tubes placed within a closed distensible bag and communicating with tubes outside of the bag, simulating the communication of the *venæ cavæ* and the aorta with the extrathoracic vessels. When such a bag is distended the tubes undergo elongation and narrowing, and their capacity is increased. The narrowed vessels also tend to be expanded, owing to the negative pressure present; and thus have their capacity further increased. The lungs in the same way, when expanded by the act of inspiration, exhibit a simultaneous elongation and narrowing of the intrapulmonary vessels, which results, however, in an increase in their total capacity.

During expiration negative intrathoracic pressure becomes less, so that there is a gradual return of the elongated and narrowed intrathoracic vessels to that condition which existed at the beginning of inspiration; at the same time the intrapulmonary vessels are not only subjected to the passive influence of the declining intrathoracic pressure, but are actively squeezed, as it were, between the air in the lungs on one side and the expiratory forces expelling the air on the other. Thus we have during expiration passive and active agents combining to bring about changes in the capacity of the intrapulmonary vessels.

The mechanical effects of the movements of respiration upon blood-press-

ure may be crudely demonstrated by Hering's device (Fig. 79). The chamber A represents the thorax; the rubber bottom B the diaphragm; C, the opening of the trachea; E D, a tube leading from the thoracic cavity to the manometer I, by means of which intrathoracic pressure is measured; G is a vessel containing water, colored blue in imitation of venous blood, communicating by means of a tube with an oblong flaccid bag F, in imitation of the heart and the intrathoracic vessels, and finally with the vessel H; V' and V are valves in imitation of valves in the heart and pulmonary vein and aorta. If now the knob K which is fastened to the centre of the diaphragm be pulled down, rarefaction of the air within the chamber occurs, so that the greater external pressure forces air through the tube C into the two rubber bags (lungs); at the same time and for the same reason water is forced from the vessel G into F, which is distended. The diaphragm upon being released is drawn up in part by virtue of its own elasticity and in part by the negative pressure within the chamber. The rubber bags are emptied by their own natural elastic reaction. At the

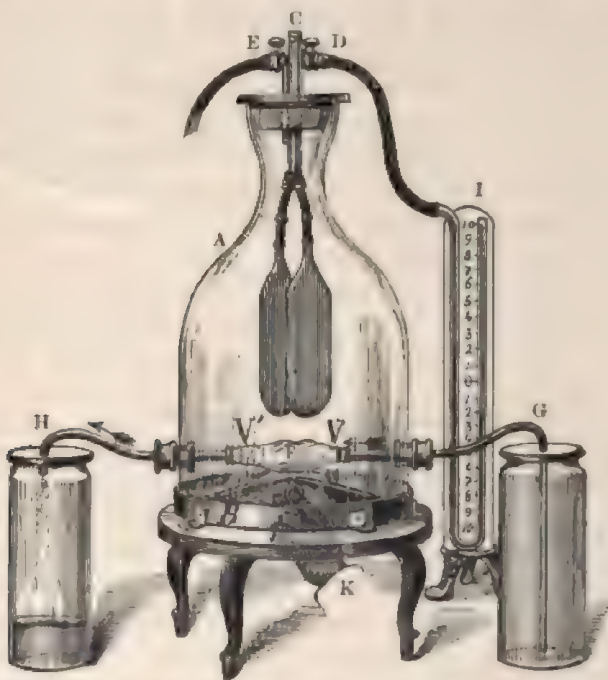


FIG. 79.—Hering's device to illustrate the influence of respiratory movements upon the circulation.

same time the distended bag F contracts on its contained fluid, forcing it into the vessel H, the valve V preventing a back-flow into G. The degree of force exerted by the traction on the diaphragm is read from the scale on the manometer.

This simple contrivance teaches us that during the entire phase of inspiration there is a condition of progressively increasing negative pressure within the thorax, and that not only is air aspirated into the lungs, but that blood is



drawn into the large, flaccid *venæ cavæ*; and that during expiration there is a gradual diminution of negative pressure during which air is expelled from the lungs and blood from the expanded *venæ cavæ*.

The increased flow into the thoracic cavity during inspiration is favored in its progress through the pulmonary vessels by the increased capacity of the lung-capillaries and by the fact that the increased negative pressure affects the thin-walled and slightly distended pulmonary veins more than the thick-walled and more distended pulmonary arteries, so that the "driving force" of the lung circulation, which is essentially the difference in pressure between the blood in the pulmonary arteries and that in the veins, is thereby increased during inspiration and the blood-current is driven with greater velocity. More blood thus being brought into the chest, and consequently to the heart, during inspiration, and less resistance being offered to the flow of the blood through the lungs, more blood must ultimately find its way to the left side of the heart, and consequently into the general circulation. If, therefore, the general capillary resistance in the systemic circulation remains the same, it is evident that an increased blood-supply to the left ventricle must cause the general blood-pressure to rise. That this rise does not become manifest immediately at the beginning of inspiration is doubtless owing to the filling of the flaccid and partially collapsed large veins and to the increased capacity of the intrapulmonary vessels. The continuance of the rise for a short time after the cessation of inspiration is due apparently to the partial emptying of the lung-vessels, whereby, owing to the arrangement of the heart-valves, the excess of blood is forced toward the left side of the heart.

Besides the above factors, the flow of blood to the right side of the heart is favored by the pressure transmitted from the conjoint actions of the diaphragm and the abdominal walls through the abdominal viscera to the abdominal vessels. The pressure upon the arteries tends to drive the blood toward the lower extremities and to hinder the flow from the heart; in the veins, however, the flow toward the heart is encouraged, while that from the extremities is hindered. The rigid walls of the arteries protect them from being materially affected, but the flaccid veins are influenced to a marked degree; while, therefore, the flow from the left side of the heart is not materially interfered with, that through the veins toward the right side is appreciably facilitated, and thus the supply of blood to the heart is increased. The effects of these movements may be seen after section of the phrenic nerves, which causes paralysis of the diaphragm, when it will be noted that the blood-pressure curves are much reduced. This diminution is attributed to two causes—the enfeebled respiratory movements, which are now confined to the ribs and the sternum, and the absence of the pressure transmitted from the diaphragm through the abdominal organs to the veins. If in such an animal the abdomen be periodically compressed, in imitation of the effects produced by the contraction of the diaphragm, the respiratory curves may be restored to their normal height.

During expiration, since the conditions are reversed the effects also must be reversed. The increased negative intrathoracic pressure occasioned by inspira-

tion now gives place to a gradual diminution, and with this a lessening of the aspiratory action due to the sub-atmospheric intrathoracic pressure; the blood-supply is further reduced because of the lessened amount of blood coming through the inferior vena cava; the abdominal veins, instead of being compressed and their contents forced chiefly toward the heart, are now being filled; finally, during the shrinkage of the lungs the intrapulmonary vessels become lessened in capacity, and thus temporarily force more blood into the left side of the heart and cause the brief rise of arterial pressure observed at the beginning of expiration.

Another factor believed by some to be involved in the respiratory undulations in blood-pressure is a rhythmical excitation of the vaso-constrictor centre in the medulla oblongata, asserted to occur coincidently with the inspiratory discharge from the respiratory centre. This has, however, been disproved. Others have held that the blood-pressure changes are due to the pressure exerted by the expanding lungs upon the heart; while others contend that rhythmical alterations in the heart-beats are important. This latter factor is of importance in man and in the dog, in which there is a distinct increase in the rate of the heart-beat during inspiration, and co-operates in producing the general rise of pressure during inspiration.

**The Effects on the Pulse.**—During inspiration the pulse-rate is more rapid than during expiration. If we cut the pneumogastric nerves, it will be seen that, while the rate is increased as the result of the section, the difference during inspiration and expiration is abolished; on the other hand, if the thorax be widely opened, but the pneumogastric nerves are left intact, the inspiratory increase in the rate still occurs. This indicates that the cardio-inhibitory centre is either less active during inspiration or more active during expiration, and that there is an associated activity of the respiratory and cardio-inhibitory centres. Why this sympathy should exist between the respiratory and cardio-inhibitory centres we do not know, but it has been suggested that during expiration the blood reaching the centres is less highly arterialized than during the inspiratory phase, and that the cardiac centre is so sensitive to the difference as to be affected, and thus its activity is somewhat increased during the expiratory phase, with the consequent decrease in the pulse-rate.

During inspiration the pulse-rate is not only higher than during expiration, but the form of the pulse-wave is affected. The systolic, diastolic, and secondary waves are smaller and the diastolic notch is more pronounced, so that the diastolic character of the curves is better marked.

**The Effects of Obstruction of the Air-passages and of the Respiration of Rarefied and Compressed Air on the Circulation.**—The blood-pressure undulations produced during quiet breathing become marked in proportion to the depth of the respiratory movements. Inspiration or expiration against extraordinary resistance—as after closing the mouth and nostrils, or respiring rarefied or compressed air—may materially modify the circulatory phenomena. When we make the most forcible inspiratory effort, the air passages being fully open, not only is there a full expansion of the lungs, but great



diastolic distention of the heart and dilatation of the intrathoracic vessels; yet, notwithstanding that this powerful aspiratory action encourages the flow of an extraordinarily large amount of blood into the thoracic vessels, the heart-beats may be very small, because intrathoracic negative pressure is so great that the thin-walled auricles meet with great resistance while contracting; in consequence, then, of this forced inspiratory effort little blood is driven through the lungs to the left auricle and by the left ventricle into the general circulation. If we make the greatest possible expiratory effort, and maintain the expiratory phase with air-passages open, the heart-beats are small, owing to the small amount of blood which flows through the *venæ cavæ* to the right auricle, and to the resistance offered by the compressed intrapulmonary vessels.

If, after a most powerful expiration, we close the mouth and nostrils and make a powerful inspiratory effort, the aspiratory effect of inspiration on the heart and the blood-vessels is manifest to its utmost degree: the heart and the vessels tend to undergo great dilatation, the blood-flow to the right auricle and ventricle is increased, the intrapulmonary vessels and the heart become engorged, and, owing to the powerful traction of the negative pressure upon the heart, especially upon the right auricle, very little blood is forced through the lungs to the left auricle and ventricle and subsequently into the general circulation, thus causing a fall of blood-pressure; indeed, the heart-sounds and the pulse may disappear. If now we make the most forcible inspiratory effort, close the glottis, and make a powerful expiratory effort, not only is the air in the lungs subjected to high positive pressure, but the heart and the great vessels partake in the pressure-effects, the blood being forced from the pulmonary circulation into the left auricle, thence by the ventricle into the aorta, with the result of a temporary rise of blood-pressure. The pressure upon the intrathoracic veins is so great that the flow of blood into the chest is almost shut off, hence the veins outside the thorax become very much distended, as seen in the superficial veins of the neck, and the heart is pressed upon to such an extent that, together with the lessened supply of blood, the heart-sounds and the radial pulse may disappear and the blood-pressure falls.

The respiration into or from a spirometer (p. 427) containing rarefied or compressed air modifies the blood-pressure curves. Inspiration of rarefied air causes a greater rise of blood-pressure than when respiration occurs at normal pressure, while during expiration, although the blood-pressure falls, it may remain somewhat above the normal. The increase of pressure is due to the aspiratory effort required to draw the air into the lungs, which effort also makes itself felt to a more marked degree upon the heart and the intrathoracic and intrapulmonary vessels, thus increasing the blood-flow through the pulmonary circulation. During expiration air is aspirated from the lungs into the spirometer, tending to dilate the intrathoracic and intrapulmonary vessels and the heart and thus to aid the pulmonary circulation. After a time, however, there is a fall of blood-pressure on account both of the engorgement of the thoracic vessels and the accompanying depletion of the general circulation, and of the distention of the heart and interference with its contractions.

Inspiration of compressed air lessens the extent of, and may prevent, the

inspiratory rise, or it may cause a fall. If, upon the respiration of compressed air, the pressure of the air be above that exerted by the elastic tension of the lungs, no effort of the inspiratory muscles is required, the chest being expanded by the pressure of the air. Therefore, instead of an increase of negative intrathoracic pressure, as in normal inspiration, there is a decrease, and negative intrathoracic pressure is replaced by positive pressure. As a result, the blood-vessels and the heart, instead of being dilated by an aspiratory action, are pressed upon, forcing the blood into the general circulation, and thus causing a transient rise of pressure, which is, however, succeeded by a fall due to obstruction to the flow of blood through the heart and the pulmonary vessels. Expiration into compressed air causes at first a transient increase of blood-pressure followed by a fall, the former being due to the forcing of some of the blood from the intrathoracic and intrapulmonary vessels into the general circulation, and the latter to obstruction to the blood-flow through the heart and the pulmonary circulation.

When individuals are exposed to compressed air, as in a pneumatic cabinet, or to rarefied air, as in ballooning, the effects on the circulation become of a very complex character, owing chiefly to the additional influences of the abnormal pressure upon the peripheral circulation; moreover, the effects of breathing against obstructions or of respiring rarefied or compressed air may be materially influenced by secondary effects resulting from excitation of the cardiac and vaso-motor mechanisms.

In *artificial respiration*, as ordinarily performed in the laboratory, air is periodically forced into the lungs by a pair of bellows or a pump, and is expelled from the lungs by the normal elastic and mechanical factors of expiration. When the lungs are inflated the pulmonary capillaries are subjected to opposing forces—the positive pressure of the air within the lungs on one hand, and the resistance of the thoracic walls on the other—so that the blood is squeezed out, thus momentarily increasing the blood-pressure, but subsequently retarding the current and consequently lowering the pressure. During expiration the pressure is removed and the blood-flow is encouraged; there is, therefore, a temporary fall during the filling of the pulmonary vessels, followed by a rise due to the removal of the obstruction. If the air is aspirated from the lungs, the rise of the pressure is augmented, owing to the further dilatation of the intrapulmonary capillaries; hence, in artificial respiration, during the inspiratory phase the blood-pressure curves are reversed, there being a primary transient rise followed by a fall, and during the expiratory phase a transient fall followed by a rise. In normal respiration the oscillations are due essentially to the changes in capacity of the intrapulmonary vessels caused essentially by the alterations in their length, while in artificial respiration the effects of these alterations are opposed and superseded by those due directly to positive intrapulmonary pressure.

#### J. SPECIAL RESPIRATORY MOVEMENTS.

The rhythmical expansions and contractions of the thorax which we understand as respiratory movements have for their object the ventilation of the



lungs. There are, however, other movements which possess certain respiratory characters, but which are for entirely different purposes, hence they are spoken of as special or modified respiratory movements. Some of these movements are purposeful in character, others are spasmodic; some are voluntary or involuntary, or possess both volitional and involitional characteristics; some are peculiar to certain species, etc. Among such movements are coughing, hawking, sneezing, laughing, crying, sobbing, sighing, yawning, snoring, gargling, hic-cough, neighing, braying, growling, etc.

In coughing a preliminary inspiration is followed by an expiration which is frequently interrupted, the glottis being partially closed at the time of the occurrence of each interruption, so that a series of characteristic sounds is caused. The air is forcibly ejected through the mouth, and thus foreign particles, such as mucus in the respiratory passages, may be expelled. Coughing may be either voluntary or reflex.

Hawking is somewhat similar to coughing. The glottis is, however, open during the expiratory act, and the expiration is continuous. The current of air is forced through the contracted passage between the root of the tongue and the soft palate. Hawking is a voluntary act.

In sneezing a deep inspiration is followed by a forcible expiratory blast directed through the nose; the glottis is open, and should the oral passage be open, which is not usually the case, a portion of the blast is forced through the mouth. Sneezing is usually a reflex act commonly excited by irritation of the fibres of the nasal branches of the fifth pair of cranial nerves. Peculiar sensations in the nose give us a premonition of sneezing; at such a time the act may be prevented by firmly pressing the finger upon the upper lip.

In laughing there is an inspiration followed, as in coughing, by a repeatedly-interrupted expiration during which the glottis is open and the vocal cords are thrown into vibration with each expiratory movement. The expirations are not as forcible as in coughing, the mouth is wide open, and the face has a characteristic expression due to the contraction of the muscles of expression.

Crying bears a close relationship to laughing—so much so that at times it is impossible to distinguish between the two; hence one may readily pass into the other, as frequently occurs in cases of hysteria and in young children. The chief differences between the two are in the rhythm and the facial expression. A secretion of tears is an accompaniment of crying, but not so of laughing, except during very hearty laughter. Crying normally is involuntary; laughing may be either voluntary or involuntary.

Sobbing, which is apt to follow a long period of crying, is characterized as being a series of spasmodic inspirations during each of which the glottis is partially closed, and the series is followed by a long, quiet expiration. This is usually involuntary, but may sometimes be arrested volitionally. In sighing there is a long inspiration attended by a peculiar plaintive sound. The mouth may be either closed or partially open. Sighing is usually voluntary.

Yawning has certain features like the preceding. There occurs a long, deep inspiration during which the mouth is stretched wide open, and there is usually a simultaneous strong contraction of certain of the muscles of the

shoulders and the back ; the glottis is wide open, and inspiration is accompanied by a peculiar sound ; expiration is short. Yawning may be either voluntary or involuntary.

In snoring the mouth is open, and the inflow and outflow of air throws the uvula and the soft palate into vibration. The sound produced is more marked during inspiration, and may even be absent during expiration. It is more apt to occur when the individual is lying on his back than when in any other posture. Snoring is usually involuntary, but it may be volitional.

In gargling the fluid is held between the tongue and the soft palate and air is expired through it in the form of bubbles.

In hiccough there is a sudden inspiratory effort caused by a spasmodic twitch of the diaphragm and attended by a sudden closure of the glottis, so that the inspiratory movement is suddenly arrested, thus causing a characteristic sound. Hiccough is sometimes not only distressing, but may be even serious or fatal in its consequences. It is especially apt to occur in cases of gastric irritation, in certain forms of hysteria, in alcoholism, in uræmia, etc.

Besides the above special respiratory movements, others are observed in certain species of animals, such as whining, neighing, braying, roaring, bellowing, bawling, barking, purring, growling, etc.

Of all these modified respiratory movements, coughing possesses to the clinician the most interest, because it not only may express an abnormal condition of some portion of the lungs, trachea, or larynx, but may indicate irritation in even remote and entirely unassociated parts. Thus, coughing may be the result of irritation in the nose, ear, pharynx, stomach, liver, spleen, intestines, ovaries, testicle, uterus, or mamma. Coughs which are not dependent upon irritation of the larynx, trachea, or lungs are distinguished as sympathetic or reflex coughs. The term "reflex" is a bad one, however, inasmuch as all coughs are essentially or solely reflex.

#### K. THE NERVOUS MECHANISM OF THE RESPIRATORY MOVEMENTS.

The movements of respiration are carried on involuntarily and automatically—that is, they recur by virtue of the activity of a self-governing mechanism. Each respiratory act necessitates a finely co-ordinated adjustment of the contractions of a number of muscles, which adjustment is dependent upon the operations of a dominating or controlling nerve-centre located in the medulla oblongata, and known as the *respiratory centre*. Besides this centre, others of minor importance have been asserted to exist in certain parts of the cerebro-spinal axis ; these centres are distinguished as *subsidiary* or *subordinate respiratory centres*. Connected with the respiratory centre are *afferent* and *efferent respiratory nerves*.

**The Respiratory Centres.**—After removal of all parts of the brain except the spinal bulb, rhythmical respiratory movements may still continue, but after destruction of the lower part of the bulb they at once cease. These facts indicate that the centre for these movements is in the medulla oblongata, and this conclusion is substantiated by the results of other experiments upon this region. According to the observations of Flourens, the respiratory centre is



located in an area about 5 millimeters wide between the nuclei of the pneumogastric and spinal accessory nerves in the lower end of the calamus scriptorius. When this region was destroyed he found that respiratory movements ceased and death ensued, consequently he termed it the *nœud vital*, or *vital knot*. The results of various investigations show, however, that Flourens' area, as well as certain other parts of the medulla oblongata that have been looked upon by others as being respiratory centres, are not such, but are largely or wholly collections of nerve-fibres which arise chiefly in the roots of the vagal, spinal accessory, glosso-pharyngeal, and trigeminal nerves, and which therefore are probably nerve-paths to and from the respiratory centre. Moreover, excitation of the *nœud vital* does not excite respiratory movements, but simply increases the tonicity of the diaphragm; nor is the destruction of the area always followed by a cessation of respiration. While the precise location of the centre is still in doubt, there is abundant evidence to justify the belief in its existence in the lower portion of the spinal bulb.

The centre is bilateral, one half being situated on each side of the median line, the two parts being intimately connected by commissural fibres, thus constituting physiologically a single centre. This union may be destroyed by section along the median line. Each half acts more or less independently of, although synchronously with, the other, and each is connected with the lungs and the muscles of respiration of the corresponding side. These facts are rendered manifest in the following observations: If a section be made in the median line so as to cut the commissural fibres, the respiratory movements on the two sides continue synchronously; if now the portion of the centre on the one side be destroyed, the respiratory movements on the corresponding side temporarily or permanently cease. If after section in the median line one pneumogastric nerve be divided, the sensory impulses conveyed from the lungs on the side of section to the corresponding half of the respiratory centre are prevented from reaching the centre, causing the movements of the respiratory muscles on the same side to be slower and the inspirations stronger as compared with those on the opposite side; if both pneumogastrics be divided, and the central end of one of the cut nerves be excited high in the neck by a strong current, the respiratory movements on the same side may be arrested, yet they may continue on the opposite side. These facts indicate that each half is in a measure independent of the other. The operations in the two parts are, however, intimately related, as shown by the fact that if the commissural fibres between the halves are intact, excitation or depression of one half is to a certain degree shared by the other. Thus, after section of one vagus not only are the respiratory movements less frequent and the inspirations stronger on the side of the section, but there is a corresponding condition on the opposite side; similarly, excitation of the central end of the cut nerve increases the respiratory rate both on the same and on the opposite side. Consequently, while there is more or less independence of the halves, the two are physiologically so intimately associated as to constitute a common or single centre.

Moreover, each of the halves may be supposed to consist of two distinct portions, one of which, upon excitation, gives rise to contraction of inspiratory

museles, the other to contraction of expiratory muscles; hence they are spoken of as inspiratory and expiratory parts of the respiratory centre, or as *inspiratory* and *expiratory centres*. Moderate excitation of the inspiratory centre causes not only contraction of inspiratory muscles, but an increase in the respiratory rate; and if the irritation be sufficiently strong, there occurs a spasmodic arrest of the respiratory movements in the inspiratory phase. On the contrary, excitation of the expiratory centre causes contraction of expiratory muscles and diminishes the respiratory rate; powerful excitation of the same centre is followed by arrest of movements in the expiratory phase. The inspiratory portion may therefore be regarded not only as being specifically connected with inspiratory muscles, but in the sense of an *accelerator centre*; and the expiratory portion may be regarded as being similarly connected with expiratory muscles, and as being an *inhibitory centre*. When the two are conjointly excited the accelerator effect prevails, because under ordinary circumstances the accelerator element of the centre seems more excitable and potent than the inhibitory; therefore, when the centre as a whole is irritated, it manifests an accelerator character.

In addition to this centre, the existence of subsidiary centres is claimed, situated both in the brain and in the spinal cord. One centre has been located in the rabbit in the *tuber cinereum*, which has been named a polypnoeic centre, because when excited the respirations are rendered extremely frequent. The sensitiveness of this centre is readily demonstrated by subjecting an animal to a high external temperature, when a marked increase of the respiratory rate follows; if now the tuber cinereum be destroyed, there occurs an immediate cessation of the accelerated movements. Another area has been located in the *optic thalamus* in the floor of the third ventricle; this centre is believed to be excited by impulses carried by the nerves of sight and hearing, and when irritated causes an acceleration of the respiratory rate, and when strongly excited arrests respiration during the inspiratory phase; hence it is regarded as an inspiratory or accelerator centre. Another centre has been located in the *anterior pair of the corpora quadrigemina*; it causes expiratory and inhibitory effects, and may therefore be placed among the expiratory or inhibitory centres. An inspiratory or accelerator centre has been recorded as existing in the *posterior pair of the corpora quadrigemina* and the *pons Varolii*. The *nuclei of the trigemini* are also said to act as inspiratory or accelerator centres. Respiratory centres are likewise claimed to exist in the *brain-cortex*. It is very doubtful, however, whether or not these so-called subsidiary respiratory centres should be regarded as being of a specific character. In any event, we cannot suppose that these centres are capable of evoking directly respiratory movements. If they exist, they are probably connected with the medullary centre, through which they exert their influence on the respiratory movements.

The existence of a respiratory centre in the *spinal cord* is also doubtful. The chief reason for the claim of its existence is that respiratory movements may for a time be observed after section of the cerebro-spinal axis at the junction of the spinal cord and bulb. In new-born animals after such section respiratory movements may continue for some time, strychnine rendering them



more pronounced. Again, animals in which respiration has been artificially maintained for a long time may, after section of the cord at the junction with the bulb, exhibit respiratory movements after artificial respiration has been suspended. The respiratory movements under these circumstances are, however, of a spasmodic character, and distinctly unlike the co-ordinated rhythmical movements observed in normal animals; the movements are rather of the nature of spasms simulating normal respirations.

*The Rhythmic Activity of the Respiratory Centre.*—The rhythmic sequence of the respiratory movements is due to periodic discharges from the respiratory centre. The cause of this periodicity is still obscure, but the fact that the rhythm continues after the combined section of the vagi and the glosso-pharyngeal nerves, of the spinal cord in the lower cervical region, of the posterior roots of the cervical spinal nerves, and of the spinal bulb from the parts above, indicates that the rhythm is inherent in the nerve-cells, and is not caused by external stimuli carried to the centre through afferent nerve-fibres. Loewy<sup>1</sup> has shown that under the above circumstances, when the centre is isolated from afferent nerve-impulses, the rhythmical activity of the centre is due to the blood, which, while acting as a continuous excitant, causes discontinuous or periodic discharges, so that, although we usually speak of the activity of the respiratory centre as being automatic—that is, not immediately dependent upon external stimuli—yet as a matter of fact the apparently automatic discharges are in reality due to the stimulation by the blood; the centre is therefore automatic only with reference to external nerve-stimulation.

The rhythm as well as the rate, force, and other characters of the discharges may be affected materially by the will and emotions; by the composition, supply, and temperature of the blood; and especially by certain afferent impulses, pre-eminently those originating in the pneumogastric nerves. As to the influence of the will and emotions, we are able, as is well known, to modify voluntarily to a certain extent the rhythm and other characters of the respirations, while the striking effect of emotions upon respiratory movements is a matter of almost daily observation. The importance of the composition of the blood is manifested by the marked effect upon the respirations when the blood is deficient in O, when it contains an excess of CO<sub>2</sub>, and during muscular activity, when in the blood there is a relative abundance of certain products resulting from muscular metabolism. If the blood-supply to the centre is diminished, as after severe hemorrhage or after clamping the aorta so as to interfere with the cerebral circulation, the respirations are less frequent and the rhythm is affected, the form of breathing having a Cheyne-Stokes character (p. 424); conversely, an increase in the blood-supply causes an increase in the rate. An increase or decrease in the temperature of the blood induces corresponding changes in the rate; thus, in fever the frequency of the movements increases almost *pari passu* with the augmentation of temperature, while if the temperature of the blood be reduced by applying ice to the carotids, the rate is lessened.

<sup>1</sup> *Pflüger's Archiv f. Physiologie*, 1889, Bd. xlii. S. 245-281.

Afferent impulses exercise an important, and practically a continuous, influence. After section of one pneumogastric nerve the respirations are somewhat less frequent; after section of both nerves the respirations become considerably less frequent and deeper and otherwise changed. If we stimulate the central end of one of these cut nerves below the origin of the laryngeal branches by a current of electricity of moderate intensity, the respiratory rate may be increased, and we may be able to restore, or even exceed, the normal frequency. The fact that section of these nerves is followed by a diminution of the rate and that excitation of the central end of the cut nerve causes an increase leads us to believe that the pneumogastric nerves are continually conveying impulses from the lungs to the respiratory centre, which impulses in some way increase the number of discharges, and thus the respiratory rate. The centre may be excited or depressed by excitation of the cutaneous nerves and the sensory nerves in general; thus, external heat accelerates, while a dash of cold water may either accelerate or inhibit, respiratory movements. Excitation of the glosso-pharyngeal nerves inhibits the respirations. Such inhibition occurs during deglutition to avoid the risk of introducing foreign bodies into the larynx. Similar respiratory inhibition may be induced by excitation of the superior laryngeal nerves, when, if the degree of irritation be sufficiently strong, complete arrest of the respiratory movements may occur. Strong irritation of the olfactory nerves and of the fibres of the trigemini distributed to the nasal chambers excites expiration and may be followed by complete inhibition of the respiratory movements; strong irritation of the optic and auditory nerves excites inspiratory activity; and irritation of the sciatic nerve causes an increase of the rate, and may or may not affect the depth of breathing.

The study of the rhythmic activity of the respiratory centre is further complicated by the fact that there is not only a rhythmic sequence of the respirations, but a rhythmic alternation of inspiratory and expiratory movements. While it is true that in ordinary quiet expiration but little of the muscular element is present, yet forced expiration is a well-defined co-ordinated muscular act. The mechanism whereby this alternation is brought about is not understood. Some believe that the pneumogastric nerves contain both inspiratory and expiratory fibres which are connected with corresponding parts of the respiratory centre and alternately convey their respective impulses to the centre, inspiratory impulses being excited during expiration and expiratory impulses during inspiration (p. 397). These impulses are, however, not indispensable to the alternation of inspiration and expiration, because these acts follow each other regularly, even after the isolation of the respiratory centre from the lungs by section of the pneumogastric nerves.

Thus we may conclude that the rhythmical discharges from the centre are due primarily to an inherent property of periodic activity of the nerve-cells constituting the respiratory centre and maintained by the blood, and that the rhythm, rate, and other characters of these discharges may be affected by the will and the emotions, by the composition, supply, and temperature of the blood, and by various afferent impulses. The chief factors are, under ordi-



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nary circumstances, the quantities of O and CO<sub>2</sub> in the blood, and the impulses conveyed from the lungs by the fibres of the pneumogastric nerves.

**The Afferent Respiratory Nerves.**—The chief of these nerves are the *pneumogastric, glosso-pharyngeal, trigeminal, and cutaneous nerves*. The important part taken by them in the regulation of the respiratory movements has frequently been alluded to in connection with the respiratory centres. Their functions, however, are of sufficient importance to demand special and detailed consideration.

The *pneumogastric nerves* are pre-eminently the most important. Their functions may be studied by comparing the phenomena before and after section of one or of both nerves, and from the results following excitation by stimuli of varying quality and strength under normal and abnormal conditions.

*Section of one* pneumogastric may be without effect or be followed by a transitory, slight diminution of the respiratory rate; by slower and deeper movements; by stronger, deeper, and longer inspirations; by unaltered or longer or shorter expirations; and probably by active expirations. These effects are transient, and the normal respiratory movements are usually restored within a half hour. *Section of both* nerves is sooner or later followed by a diminution of the respiratory rate; by slow, deep, powerful inspirations; by active expiration; and by a pause between expiration and inspiration. The immediate results are variable unless certain precautions are taken to prevent irritation of the central ends of the cut nerves. If the ends are allowed to fall back into the wound, the respirations may become irregular; or they may be less frequent, with weakened inspirations, spasmodic expirations, and prolonged expiratory pauses. The explanation of these variable results is found in the fact that the expiratory fibres are more sensitive to *very weak* stimulus than the inspiratory fibres, and that the mechanical irritation caused by the section, and the excitation due to the electric current in the cut ends of the nerves that is established when the central end of the nerve is replaced in the wound, excite expiratory impulses and cause expiratory phenomena; if the irritation be stronger, both inspiratory and expiratory impulses are excited, thus causing uncertain results, varying as one or the other is the stronger. If irritation be prevented, section is at once followed by typical slow, deep respirations.

*Stimulation of the central end* of the cut vagus, the other nerve being intact, is followed by variable results dependent upon the character of the stimulus. Chemical stimuli, such as a solution of sodium carbonate, excite the expiratory fibres; mechanical stimuli, the inspiratory fibres; electrical stimuli, expiratory or inspiratory fibres or both, according to the strength of the current. Single induction shocks are without effect, but a tetanizing current is very effective. Should that current which will elicit the least response be used, the breathing is rendered less frequent, the inspirations are weakened, and the expirations may be active and lengthened; in other words, there are present the same phenomena which often immediately follow section of both nerves when the cut ends are allowed to fall back into the wound and

thus establish an exciting electric current which affects expiratory fibres. If the strength of the current be increased, these effects give place to those of an opposite character, the respirations becoming more frequent and the inspirations more marked in depth and force, the explanation of this difference being that the stronger current has also excited inspiratory fibres, so that now both expiratory and inspiratory impulses are generated, but the latter, being more potent in their influences, cause acceleration of the rate and accentuated inspirations. The effects following stimulation of the central end of the cut vagus by a current of moderate strength are best observed after both nerves have been divided and when there exist slow, deep, powerful respirations. Under such circumstances stimulation of the central end of one of the vagi is followed at once by an increase in the respiratory rate and a return of the general characters of the inspiratory and expiratory phases toward the normal; and if the degree of excitation be properly adjusted, the normal rate and normal character of breathing may be restored. Still stronger excitation further accelerates the rate, causing the respiratory acts to follow each other with such frequency that inspiration begins before the expiratory act (relaxation of the inspiratory muscles) has been completed. The inspiratory muscles are therefore never completely relaxed. With a further increase of stimulus the expiratory relaxation becomes less and less, until finally the respirations are brought to a standstill in the inspiratory phase, the inspiratory muscles being in tetanus.

If the nerves be fatigued from over-excitation or if the animal be thoroughly chloralized, stimulation of the central end of the cut nerve by a strong current is no longer followed by inspiratory stimulation, but is followed by expiratory stimulation (the inspirations being shortened and weakened, the expirations prolonged and spasmodic) and by long pauses between expiration and inspiration. If the excitation be sufficiently strong, arrest of respiration occurs in the expiratory phase.

It will be observed from the above results that electrical irritation of the central end of the cut pneumogastric may be followed by effects of an opposite character, extremely weak irritation causing expiratory stimulation (weaker and shorter inspirations, prolonged and active expirations, expiratory pauses, and diminished respiratory rate); whereas moderate irritation causes inspiratory stimulation (stronger and deeper inspirations and increased respiratory rate). These diverse results are explained by the fact that these nerves contain two kinds of fibres having opposite functions: fibres of one kind convey impulses which affect the expiratory centre; those of the other kind convey impulses which affect the inspiratory centre. The former are more susceptible to weak electrical stimulation, and thus their presence may be elicited by the weakest stimulus capable of causing any response. At the same time they are less readily exhausted, so that if the vagi be subjected to prolonged stimulation by a strong current, the inspiratory fibres are exhausted before the expiratory fibres. For moderate and strong currents the inspiratory fibres are affected to a greater degree than the expiratory fibres, therefore inspiratory stimulation predominates.



Both sets of fibres convey impulses which have their origin essentially in the peripheries of the pneumogastric nerves in the lungs; but expiratory impulses may arise in the fibres of the superior and inferior laryngeal nerves, especially in the former. The impulses which arise in the lungs are under ordinary circumstances produced mechanically by the movements of the lungs, although it is believed by some that the composition of the gases in the alveoli is an important factor. According to the latter view, when the lungs are in the expiratory phase the accumulation of  $\text{CO}_2$  in the air-cells excites the peripheries of the inspiratory fibres, thus giving rise to impulses which are carried to the inspiratory portion of the respiratory centre and excite inspiration; whereas the stretching of the lungs during inspiration is held to excite the peripheries of the expiratory fibres, generating impulses which are conveyed to the expiratory portion of the respiratory centre, causing expiration. There is, however, no sufficient evidence to lead us to believe that the presence of  $\text{CO}_2$  in normal percentages influences in any way either set of fibres. On the contrary, the mechanical effects of the movements of the lungs are of great importance, as is apparent from the fact that inflation excites active expiration, whereas aspiration or collapse excites inspiration; moreover, if the movements of one lung be prevented by occlusion of the bronchi or by free opening of the pleural sac, the effects are the same as though the vagus of the same side were cut; if now the other nerve be severed, the results are the same as when both nerves are cut. The movements of the lungs therefore generate alternate inspiratory and expiratory impulses, collapse causing inspiratory impulses, and expansion causing expiratory impulses. The inspiratory impulses, however, not only excite inspiration, but concurrently limit the duration of expiration; while the expiratory impulses excite expiration and concurrently limit inspiration.

Excitation of the *superior laryngeal nerve* causes expiratory stimulation, and there may occur respiratory arrest in the expiratory phase. These fibres are extremely sensitive; and they are of considerable physiological importance, as is illustrated by the fact that the entrance of foreign bodies into the larynx during deglutition causes an immediate arrest of inspiration, and even a forced, spasmodic expiration. The foreign particles, coming in contact with the keenly sensitive fibres of these nerves, generate impulses which arrest inspiration, thus being prevented from being carried to the lungs.

The fibres of the *glosso-pharyngeal nerves* act similarly. Their excitation is followed by an arrest of respiration which lasts for a period equal to that occupied by about three of the preceding respiratory acts. The value of such an inhibitory influence is obvious: During swallowing breathing is arrested, evidently for the purpose of preventing the aspiration of food and drink into the larynx. This act is purely reflex, and is due to the excitation of fibres of these nerves by the fluid or the bolus of food after the act of deglutition has begun. Such impulses flow to the respiratory centre, immediately arresting the inspiratory discharge in whatever phase the inspiratory movement may

happen to be. When swallowing has been accomplished the inhibitory influence is removed and respiration is resumed.

The inhalation of irritating gases may cause respiratory arrest by exciting either the sensory fibres of the *trigeminal nerves* in the nose or the pneumogastric fibres in the larynx and lungs. Some gases affect the former, some the latter, others both. In the rabbit, for example, the introduction of tobacco-smoke into the lungs through a tracheal opening produces no effect upon the respirations, but if injected into the nose respiration is at once arrested. When ammonia is similarly introduced into the lungs the respirations may be either accelerated or diminished, and may be arrested in the inspiratory or the expiratory phase, but when drawn into the nose expiratory arrest follows. Some irritating gases arrest respiration in the inspiratory phase, others in the expiratory phase. Odorous gases which are powerful and disagreeable may similarly cause arrest by acting upon the *olfactory nerves*. Excitation of the *splanchnic nerves* causes expiratory arrest; stimulation of the *sciatic* and *sensory nerves* in general usually increases the number of respirations, yet under certain circumstances it may cause a decrease and final arrest during expiration.

Stimulation of the *cutaneous nerves*, as by a cold douche, slapping, etc., causes primarily a tendency to an increase in the number and depth of the respirations, but finally causes cessation in the expiratory phase. It is stated that excitation of these nerves is more effective in causing respiratory movements than irritation of the vagi. The influence of external heat is very powerful, and is perhaps the most potent means, under ordinary circumstances, of exciting the respiratory centre. The respiratory movements caused by cutaneous irritation, are, however, of the character of reflex spasms rather than of normal movements, and when the excitation is sufficiently strong the movements may be distinctly convulsive.

Finally, afferent (intercentral) fibres connect the *brain-cortex*, and probably the ganglia at the base of the brain, with the respiratory centres.

**The Efferent Respiratory Nerves.**—During ordinary respiration the only efferent or motor nerves necessarily involved are the *phrenics*, and certain other of the *spinal nerves*, and the *pneumogastrics*. Section of one phrenic nerve causes paralysis of the corresponding side of the diaphragm; section of both phrenics is followed by paralysis of the entire diaphragm. So important are these nerves in respiration that in most cases after section death occurs from asphyxia within several hours. In such cases not only is the work of inspiration thrown upon the other inspiratory muscles, but the effectiveness of the latter is greatly compromised by the relaxed condition of the diaphragm, which permits of its being drawn into the thoracic cavity with each inspiration, thus hindering the expansion of the lungs. If section be made of the spinal cord just below the exit of the fifth cervical nerve, costal movements cease, but diaphragmatic contractions continue. The level of the section is just below the origin of the roots of the phrenics, so that the motor fibres for the diaphragm are left intact, but the motor impulses which would have gone out to other inspiratory muscles



through the spinal nerves below the point of section are cut off. If the cord be cut just below the medulla oblongata or above the origin of the phrenics, both costal and diaphragmatic movements immediately or very soon cease, but respiratory movements may continue in the larynx, and when dyspnoea occurs they may be observed in the muscles of the face, neck, and mouth. In rare cases, after section at the junction of the medulla oblongata and the spinal cord, respiratory movements may continue in the thorax and the abdomen, but these instances are exceptional and the movements are of the nature of reflex spasms.

During each respiratory act there flow to the larynx impulses which open the glottis during inspiration. The pathway of these impulses is through the laryngeal branches of the vagi, almost solely through the recurrent or inferior laryngeal nerves. (See section on the Physiology of the Voice.) If the pneumogastrics are cut above the origin of these branches, respiratory movements in the larynx cease, and, owing to the paralysis of the laryngeal muscles, the vocal cords are flaccid, the glottis is no longer widened, and thus great resistance is offered to the inflow of air, causing difficulty during inspiration.

During forced breathing, besides the above nerves a number of others may be involved, especially the *spinal nerves*, which supply the extraordinary respiratory muscles of the chest, abdomen, pelvis, and vertebral column, and the *facial, hypoglossal, and spinal accessory nerves*.

#### L. THE CONDITION OF THE RESPIRATORY CENTRE IN THE FETUS.

During intra-uterine life the child receives O from and gives CO<sub>2</sub> to the blood of the mother. No attempt is made by the child to breathe, because the centre is in an apnoæic condition, due to a low condition of irritability and to the relatively large amount of O in the blood. The fetal blood contains a larger percentage of hæmoglobin than the blood of the mother; Quinquaud has shown that the fetal blood has a larger respiratory capacity than adult's blood; and Regnard and Dubois have proven the same to be true of the calf and the cow. Were it not for these two conditions, the child would continually attempt to breathe. While such efforts do not occur under normal circumstances, they may be present if we interfere in any way with the supply of oxygen, as by pressure upon the umbilical vessels. The child has been seen to make respiratory efforts while within the intact fetal membranes. It seems evident, therefore, that all that is necessary to excite the respiratory centre to activity is a venous condition of the blood. *In utero*, and as long as the child is bathed in the amniotic fluid, respiratory movements cannot be carried on even though the respiratory centre be excited to activity, the reason being that with the first movement of inspiration amniotic fluid is drawn into the nasal chamber; the fluid acts as a powerful excitant to the sensory fibres of the mucous membrane, thus causing inhibitory respiratory impulses. From this fact we learn the practical application that it is desirable immediately after birth of a child, if spontaneous respirations do not immediately and effectively occur, to carefully remove mucus or other matter from the nose, so that the inhibitory influences generated by nasal irritation shall be discontinued.

When the exchange of O and CO<sub>2</sub> is interfered with for a long period, as in cases of prolonged labor, the respiratory centre may become so depressed that spontaneous respirations do not occur upon the birth of the child. In such a case respirations may usually be initiated by irritation of the skin, as by slapping, sprinkling with ice water, etc. Respirations may also be carried on successfully by artificial means (see p. 446).

*In utero* the lungs are devoid of air; the sides of the alveoli and of the small air-passages are in apposition, although the lungs completely fill the compressed thoracic cavity. During the first inspiration comparatively little air is taken into the lungs, because of the force necessary to overcome the adhesion of the sides of the alveoli and of the smaller air-tubes, but as one inspiration follows another inflation increases more and more until full distention is accomplished. The vigorous crying which so generally occurs immediately after birth doubtless is of value in facilitating this expansion. If once the lungs have been filled with air, they are never completely emptied of it, either by volitional effort or by collapse after excision.

#### M. THE INNERVATION OF THE LUNGS.

The nerves of the lungs are derived from the *pneumogastrics*, the *sympathetics*, and the *upper dorsal nerves*. Scattered along the paths of distribution of these fibres are many small *ganglia*.

*The Pneumogastric Nerves.*—The pulmonary branches of the pneumogastric nerves contain not only fibres which convey impulses that affect the general characters of the respiratory movements, but other fibres that are of great importance to the respiratory mechanism. Setting aside the effects on the respiratory movements following section and stimulation of one or of both vagi, there are observed phenomena which are of an entirely different character, and which are due to excitation or paralysis of certain other specific nerve-fibres. Among these fibres are efferent and afferent *broncho-constrictors* and *broncho-dilators*. Roy and Brown<sup>1</sup> found in investigations upon dogs that stimulation of one vagus caused constriction of the bronchi in both lungs; section of one vagus was followed by expansion of the bronchi in the corresponding lung, which expansion was sometimes preceded by a slight contraction owing to the temporary irritation caused by the section; stimulation of the peripheral end of the cut nerve caused a contraction of the bronchi in both lungs; stimulation of the central end of the cut nerve was followed by a contraction of the bronchi in both lungs, but not so marked as when the peripheral end was stimulated; stimulation of sensory nerves other than the vagus rarely, and then only to a slight extent, caused contraction; atropine paralyzed the constrictor fibres; nicotine in small doses had a powerful expansive effect on the bronchi; after etherization stimulation of either the central or the peripheral end of the cut pneumogastric nerve was often followed by broncho-dilata-

<sup>1</sup> *Journal of Physiology*, vol. 6, 1885 (*Proceedings of the Physiological Society*, iii. p. xxi.); Einthoven, *Pflüger's Archiv für Physiologie*, 1892, Bd. 51, S. 367; Sandeman, *Du Bois-Reymond's Archiv für Physiologie*, 1890, S. 252.



tion; asphyxia causes broncho-constriction, but not after section of the pneumogastric nerves; after section of both vagi it is impossible to cause reflex broncho-constriction or broncho-dilatation; the constriction of the bronchi may be so great as to reduce their calibres to one-half or one-third, or even more. The above results are very instructive, and show—(1) That broncho-constriction or broncho-dilatation can be obtained by stimulating the peripheral end of the vagus, and that these changes occur in the bronchi of both lungs when only one nerve is excited, thus proving that each nerve supplies both kinds of fibres to both lungs; (2) that the same results can be obtained by excitation of the central end of the cut nerve, thus showing that the pneumogastrics contain both afferent constrictor and afferent dilator fibres; (3) that reflex broncho-constriction and broncho-dilatation cannot be produced after section of the vagi, thus proving that all of the efferent fibres pass through the pneumogastrics; (4) that asphyxia and the inhalation of  $\text{CO}_2$  cause broncho-constriction, but not after section of the vagi, thus indicating that under these circumstances the effects on the bronchi are reflex; (5) that certain poisons affect one or the other of these two sets of fibres.

The presence of *efferent vaso-motor* fibres in the vagi has been disproved by the results of experiments by Bradford and Deau,<sup>1</sup> and others. These observers have shown, however, that the vagi contain *afferent pressor* fibres, irritation of which is followed by constriction of the pulmonary vessels that may or may not be accompanied by constriction of the systemic vessels, the efferent fibres in this case reaching the lungs through the sympathetic nerves.

The existence of *trophic* fibres is generally admitted. After section of one pneumogastric nutritive changes immediately begin in the lung of the corresponding side, which changes are manifest in the appearance of inflammation in the middle and lower lobes. Section of both nerves is followed by inflammation in the middle and lower lobes of both lungs.

The vagi contain *sensory* fibres for the larynx, trachea, and lungs, after section of which fibres there is an absolute loss of sensibility in these parts.

It is probable that the vagi contain *secretory* fibres for the mucous glands.

Thus we find that the pneumogastric nerves supply the lungs with (1) afferent *inspiratory* and *expiratory* fibres; (2) afferent and efferent *broncho-constrictor* and *broncho-dilator* fibres; (3) afferent *pressor* fibres; (4) general *sensory* fibres; (5) *trophic* fibres; (6) and probably *secretory* fibres for the mucous glands.

*The Sympathetic Nerves.*—The sympathetics supply *trophic* and efferent *vaso-motor* fibres. The efferent vaso-motor fibres pass from the spinal cord in the anterior roots of the second to the seventh dorsal nerve, inclusive, to join the sympathetics, thence through the first thoracic ganglia to the lungs.

*The Ganglia.*—Nothing is known of the functions of the ganglia.

<sup>1</sup> *Journal of Physiology*, 1894, vol. 16, p. 70.

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Mammals.		Birds.		Reptiles and Fish. <sup>1</sup>	
	Centigrade.		Centigrade.		Centigrade.
Mouse . . . . .	41.1°	Birds . . . . .	44.03°	Frog . . . . .	0.32-2.44°
Sheep . . . . .	37.3-40.5°	Duck . . . . .	42.50-43.90°	Snakes . . . . .	2.5-12.0°
Ape . . . . .	35.5-39.7°	Goose . . . . .	41.7°	Fish . . . . .	0.5-3.0°
Rabbit . . . . .	39.6-40.0°	Gull . . . . .	37.8°	Invertebrates <sup>1</sup>	
Guinea-pig . . . . .	38.4-39.0°	Guinea . . . . .	43.90°	Crustacea . . . . .	0.6°
Dog . . . . .	37.4-39.6°	Turkey . . . . .	42.70°	Cephalopods . . . . .	0.57°
Cat . . . . .	38.3-38.9°	Sparrow . . . . .	39.08-42.10°	Medusæ . . . . .	0.27°
Horse . . . . .	36.8-37.5°	Chicken . . . . .	43.0°	Polyps . . . . .	0.21°
Rat . . . . .	38.8°	Crow . . . . .	41.17°	Mollusca . . . . .	0.46°
Ox . . . . .	37.5°				
Ass . . . . .	36.95°				

The Temperature of the Different Regions of the Body.—The quantities of heat produced and dissipated by different parts of the economy vary, consequently there must continually be a transmission of heat from the warmer to the cooler parts to establish throughout the organism an equilibrium of temperature. Heat is distributed by direct conduction from part to part, but probably chiefly by the circulating blood and lymph. These means of distribution are, however, not sufficiently active to establish a uniform temperature. Thus we find that the internal parts of the body have a higher temperature than the external parts; that some internal organs are considerably warmer than others; that every organ is warmer when active than when at rest; that the temperature varies in different regions of the surface of the body, etc. The following figures by Kunkel<sup>2</sup> instance some of these differences, the temperature of the room being 20° C.:

	Centigrade.		Centigrade.
Forehead . . . . .	34.1°-34.4°	Sternum . . . . .	34.4°
Cheek under the zygoma . . . . .	34.4°	Pectorales . . . . .	34.7°
Tip of ear . . . . .	28.8°	Right iliac fossa . . . . .	34.4°
Back of hand . . . . .	32.5°-33.2°	Left iliac fossa . . . . .	34.6°
Hollow of the hand (closed) . . . . .	34.8°-35.1°	Os sacrum . . . . .	34.2°
Hollow of the hand (open) . . . . .	34.4°-34.8°	Eleventh rib (back) . . . . .	34.5°
Forearm . . . . .	33.7°	Tuberosity of ischium . . . . .	32.0°
Forearm (higher) . . . . .	34.3°	Upper part of thigh . . . . .	34.2°
		Calf . . . . .	33.6°

The temperature of the skin is higher over an artery than at some distance from it; it is higher over muscle than over sinew; it is higher over an organ in activity than when at rest; it is higher in the frontal than in the parietal region of the head, and on the left side of the head than on the right, etc.

Temperature observations are usually made in the rectum, in the mouth under the tongue, in the axilla, and in the vagina, the rectum being preferable, although in the human being the temperature is usually obtained in the mouth and axilla. In the same individual when records are taken simultaneously in all four regions appreciable differences will be noted. The temperature in the axilla is, according to Hunter 37.2° C., to Davy 37.3° C., to Wunderlich 36.5° to 37.25° C. (mean 37.1° C.), to Liebermeister 36.89° C., to Jürgensen 37.2° C.,

<sup>1</sup> Temperatures above that of the surrounding medium.  
<sup>2</sup> *Zeitschrift für Biologie*, 1889, Bd. 25, S. 69-73.

and to Jaeger 37.3° C. The mean axillary temperature may be put down as being about 37.1° C. (98.8° F.), the normal limits being 36.25° to 37.5° C. (97.2° to 99.5° F.) The temperature in the mouth is about 0.2° to 0.5° C. higher than in the axilla, in the rectum from 0.3° to 1.5° C. higher, and in the vagina from 0.5° to 1.8° C. higher.<sup>1</sup>

The temperature of different tissues varies. Davy, as results of observations on a fresh-killed sheep, gives the temperature of the brain as about 40° C.; of the left ventricle 41.67° C.; of the right ventricle 41.11° C.; of the liver 41.39° C.; of the rectum 40.56° C. According to Bernard, the liver is the warmest organ in the body, and then the following in the order named—brain, glands, muscles, and lungs.

The temperature of the blood varies considerably in different vessels. In the carotid it is from 0.5° to 2° C. higher than in the jugular vein; in the crural artery, from 0.75° to 1° C. higher than in the corresponding vein; in the right side of the heart about 0.2° C. higher than in the left; in the hepatic vein 0.6° C. higher than in the portal vein during the intervals of digestion, and as much as 1.5° to 2° C. or more during periods of digestion; the venous blood coming from internal organs is warmer than the arterial blood going to them, but the blood coming from the skin is cooler than that going to it; the blood coming from a muscle in a state of rest is about 0.2° C., and during activity as much as 0.6° to 0.7° C., warmer than that supplied to the muscle. The mean temperature of the blood as a whole is about 39° C. (102° F.); of venous blood about 1° C. (1.8° F.) lower than of arterial blood. The warmest blood in the body is that coming from the liver during the period of digestion; the coolest blood is that coming from the tips of the ears and nose and similarly exposed parts.

**Conditions affecting Bodily Temperature.**—The mean temperature of the body is subjected to variations which depend chiefly upon age, sex, constitution, the time of day, diet, activity, season and climate (surrounding temperature), the blood-supply, disease, drugs, the nervous system, etc.

The temperature of a new-born child (37.86° C.) is from 0.1° to 0.3° C. higher than that of the vagina of the mother; it falls about 1° C. during the first few hours after birth, and then rises within the next twenty-four hours to about 37.4° to 37.5° C. The mean temperature of an infant a day or two old is about 37.4° C. It very slowly sinks until full growth is attained, when the normal mean temperature of adult life is reached (37.1° C.), a standard which is maintained until about the age of forty-five or fifty, when it declines until about the age of seventy (36.8° C.), and then slowly rises and approaches in very old people (eighty to ninety years) the temperature of very young infants (37.4° C.). It is important to observe that during the early weeks of life the temperature may undergo considerable variations, and that it is readily affected by bathing, exposure, crying, pain, sleep, etc., and by many circum-

<sup>1</sup> The average figures of the mean daily temperatures obtained from the records of a number of investigators are, mouth, 36.87°; axilla, 36.94°; and rectum, 37.02°. The mean figures for the twenty-four hours are in each case about 0.2° less.



stances which have little or absolutely no influence upon the temperature of the adult.

The mean temperature of the female is said to be slightly lower than that of the male. In observations on children Sommer noted a difference of  $0.05^{\circ}$  C., and Fehling a difference of  $0.33^{\circ}$  C.

Individuals with vigorous constitutions have a somewhat higher temperature than those who are weak.

Records obtained by various European investigators indicate that the bodily temperature is subjected to regular diurnal variations. The limits of variation in health are from  $1^{\circ}$  to  $2^{\circ}$  C. The maximum temperature observed is usually from 5 to 8 P. M. (mean, about 7 P. M.); the minimum, from 2 to 6 A. M. (mean, about 4 A. M.). Carter's<sup>1</sup> experiments on rabbits, cats, and dogs show that rhythmical temperature-changes occur in these animals which agree with those noted by Jürgensen in man. This same rhythm is stated to occur during fasting, so that the ingestion and the digestion of food cannot be claimed to account for it; moreover, it is present in fever and not disturbed by muscular activity and by cold baths. If an individual works at night and sleeps during the day, thus reversing the prevailing custom, the temperature curve is more or less modified, but, according to Mosso,<sup>2</sup> not reversed as stated by Krieger.<sup>3</sup> Chelmonski found, however, in old persons that the temperature variations are not uncommonly inverted, being higher in the morning and lower in the evening.

Insufficient diet causes a lowering of the temperature; a liberal diet tends to cause a rise slightly above the normal mean, especially during forced feeding or when the food is particularly rich in fats and carbohydrates. There is a rise during digestion which is usually slight, but it may reach  $0.2^{\circ}$  or  $0.3^{\circ}$ , the increase being due chiefly to the activity of the intestinal muscles (see p. 431). Although considerably more heat is produced during the periods of digestion than during the intervals, the excess is dissipated almost as rapidly as it is formed, so that but little heat is permitted to accumulate and thus cause a rise of temperature. Hot drinks and solids tend to augment, and cold drinks and solids to lower bodily temperature. In the nursing child Demme found that the rectal temperature sinks during the first half-hour after taking food, then rises during the next sixty to ninety minutes to a point from  $0.2^{\circ}$  to  $0.8^{\circ}$  C. higher than the temperature before feeding, and falls again during the next thirty to sixty minutes.

All conditions which increase metabolic activity are favorable to an increase of temperature. Thus, during the activity of the brain, glands, muscles, etc., more heat is produced than when the tissues are at rest; indeed, so abundant is heat-production during severe muscular exercise that the temperature of the body may rise as much as  $0.5^{\circ}$  to  $1.5^{\circ}$  C. ( $1^{\circ}$  to  $2.7^{\circ}$  F.). During sleep the temperature falls from  $0.3^{\circ}$  to  $0.9^{\circ}$  C. or more in young children.

<sup>1</sup> *Journal of Nervous and Mental Diseases*, 1890, vol. xvii. p. 782.

<sup>2</sup> *Archives italiennes de biologie*, 1887, t. viii. p. 177.

<sup>3</sup> *Zeitschrift für Biologie*, 1869, Bd. v. S. 479.

During the summer the mean bodily temperature is from  $0.1^{\circ}$  to  $0.3^{\circ}$  C. higher than during the winter. In warm climates it is about  $0.5^{\circ}$  C. higher than in cold climates, but the difference is not due to race, since it is observed in individuals who have changed their habitations from one climate to another. Continued exposure to excessively high or low temperatures is inimical to life. Exposure in dry air at a temperature of  $100^{\circ}$  to  $130^{\circ}$  C. may cause the bodily temperature to increase as much as  $1^{\circ}$  to  $2^{\circ}$  C. within a few minutes, and the temperature may rise so rapidly as to cause fatal symptoms within ten or fifteen minutes. A hot moist air is far more oppressive and dangerous than hot dry air.

Baths exercise a potent influence on bodily temperature, hot baths increasing and cold baths decreasing it. The effect of a cold bath is less if it follows a hot bath. Thus Dill<sup>1</sup> found that his morning temperature varied from  $33.7^{\circ}$  to  $36.6^{\circ}$  C., after a hot bath ( $40^{\circ}$ – $41^{\circ}$  C.) it rose, in one instance, as high as  $39.5^{\circ}$  C., and after a cold bath it remained at  $37^{\circ}$  C. When, however, the hot bath was omitted the cold bath reduced the temperature to  $35.4^{\circ}$  C. Baljakowski<sup>2</sup> has recorded some very interesting results which show that the local application of heat causes the bodily temperature to sink and the cutaneous temperature of the part experimented upon to rise. The experiments were conducted on young men, whose arms and legs were encased in hot sand at a temperature of  $55^{\circ}$  C. When the arm was used the axillary temperature sunk an average of  $0.13^{\circ}$  C. during the bath and subsequently  $0.24^{\circ}$  C., the corresponding records of average rectal temperature being  $0.23^{\circ}$  and  $0.31^{\circ}$  C. In case of the leg bath the corresponding records were axillary  $0.06^{\circ}$  and  $0.32^{\circ}$  C.; and rectal  $0.21^{\circ}$  and  $0.25^{\circ}$  C. The cutaneous temperature of the limb experimented upon increased materially, the average rise varying from  $0.73^{\circ}$  to  $1.20^{\circ}$  C., according to the part of the limb. Long-continued severe external cold may prove fatal, but this is not necessarily due to the effect on bodily temperature, for Milne-Edwards<sup>3</sup> has shown that rabbits die within five or six days when exposed to a temperature of  $-10^{\circ}$  to  $-15^{\circ}$  C., without the bodily temperature falling more than  $1^{\circ}$  C.

There is a general relationship between the frequency of the heart's beat and the bodily temperature, especially in fever. Bärensprung noted such a coincidence between the diurnal variations of the pulse and bodily temperature; and, in fever, Aiken found that for each increase of  $0.55^{\circ}$  C. ( $1^{\circ}$  F.) above the mean normal temperature the pulse-rate was increased about ten beats per minute. But the variations in the two do not always correspond either quantitatively or qualitatively. Liebermeister found in man that for a rise of each degree from  $37^{\circ}$  to  $42^{\circ}$  C. the increase in the pulse-rate was 12.6, 8.6, 8.7, 11.5, and 27.5 beats per minute respectively. Beljakowski's<sup>4</sup> experiments show that the bodily temperature may fall and the pulse-rate rise—in one set of experiments the rectal temperature falling on an average  $0.23^{\circ}$  C. and the pulse increasing

<sup>1</sup> *British Medical Journal*, 1890, vol. i. p. 1136.

<sup>2</sup> *Vratch*, 1889, p. 436; *Provincial Medical Journal*, 1890, p. 113.

<sup>3</sup> *Comptes rendus de la Soc. de Biologie*, 1891, t. 112, pp. 201–205.

<sup>4</sup> *Loc. cit.*



on an average 6.85 beats per minute. After the local hot bath the temperature remained subnormal, and the heart-beats became less frequent, and finally were on an average from 2.7 to 3.1 beats per minute less than the normal rate.

More important, however, than the pulse-rate is the effect of the amount of blood supplied to any given part of the body. The mere lowering or raising of the arm is sufficient to alter the blood-supply to the part; thus Römer found that keeping the arm elevated for five minutes was sufficient to reduce the temperature of the hand  $0.19^{\circ}$  C., and that if the period was doubled the fall amounted to  $0.38^{\circ}$  C. Compression of the veins of the arm may diminish the temperature of the hand as much as  $0.25^{\circ}$  to  $2.45^{\circ}$  C., while compression of the brachial artery may cause a fall of  $2.4^{\circ}$  within fifteen minutes. A larger supply of blood to the cutaneous surface increases cutaneous temperature and tends to decrease internal temperature, while a lessened supply causes the opposite effects.

In abnormal conditions the temperature may be increased or decreased: in cholera, diabetes, and in the last stages of insanity, it may be lowered  $6^{\circ}$  or  $8^{\circ}$  C. or even more. In fever it is increased, usually ranging between  $37.5^{\circ}$  and  $41.5^{\circ}$  C. ( $99.4^{\circ}$  and  $106.7^{\circ}$  F.), but in very rare cases it may reach  $44^{\circ}$  to  $45^{\circ}$  C. ( $111^{\circ}$  to  $113^{\circ}$  F.) just before death. A temperature of  $42.5^{\circ}$  C. ( $108.5^{\circ}$  F.) maintained for several hours is almost inevitably fatal. In frogs, the highest temperature consistent with life for any length of time is below  $40^{\circ}$  C.; in birds, from  $48^{\circ}$  to  $50^{\circ}$  C., and in dogs, from  $43^{\circ}$  to  $45^{\circ}$  C. Exceptional cases are on record of people having survived extraordinarily high or low bodily temperature, Richet having reported one in which the temperature several times was  $46^{\circ}$  C. ( $114.8^{\circ}$  F.), while Teale records an axillary temperature of  $50^{\circ}$  C. ( $122^{\circ}$  F.) in an hysterical (?) woman. Fräntzel noted a temperature of  $24.4^{\circ}$  C. ( $76.2^{\circ}$  F.) in a drunken man, and Kosürew a temperature of  $26.5^{\circ}$  C. ( $79.7^{\circ}$  F.) in a man having a fractured skull.

Bodily temperature may be variously influenced by drugs and other substances, micro-organisms, etc. Some increase it, others decrease it, others are without any marked influence, while others exert primary and secondary actions. Among those which increase bodily temperature are cocaine, atropin, strychnin, brucin, caffeine, veratrin, etc., and, as shown by Krehl<sup>1</sup> and others, a large number of other organic substances and micro-organisms. Temperature is decreased by anesthetics, morphin and other hypnotics, quinin, various antipyretics, large doses of alcohol, etc.

Among the most important of the conditions which affect bodily temperature are disturbances of the nervous system. Injury or irritation of almost any part of the nerve centres and of certain nerves may give rise directly or indirectly to alterations of temperature, and there are some parts which are very sensitive in this respect, especially certain areas of the brain cortex, the striated bodies, the pons Varolii, the spinal bulb, and the cutaneous nerves. The results of injury or stimulation of these as well as of other parts will be considered later on (p. 493).

<sup>1</sup> *Arbeiten für experimentelle Pathologie und Pharmacologie*, 1895, Bd. 35, S. 222-268.

**Temperature-regulation.**—The fact that during life the organism is *continually* producing and losing heat, and that the bodily temperature of homo-thermous animal is maintained at an almost uniform standard, notwithstanding considerable mutations of surrounding temperature, renders it evident that there exists an important mechanism whereby the regulation of the relations between heat-production and heat-dissipation is effected. It must be evident that when the variations in heat-production and heat-dissipation balance, bodily temperature must remain unaltered, and that if the changes in one exceed those in the other the temperature rises or falls, depending upon whether more or less heat is produced than is dissipated. It does not follow that because heat-production is increased the bodily temperature must similarly be affected, since heat-dissipation may be increased to the same extent and thus effect a compensation. Therefore an alteration in heat-production or in heat-dissipation by no means implies that the temperature must be affected. Moreover, when the temperature is increased or diminished the change may be caused by various alterations in the quantities of heat produced or lost, singly or combined, and the temperature may remain constant even when both processes are materially affected. Thus, the temperature remains *constant* when both heat-production and heat-dissipation are normal, and when both are increased or decreased to the same extent. The temperature is *increased* when heat-production is normal and heat-dissipation diminished; when both heat-production and heat-dissipation are diminished, but when heat-production is diminished to a less extent than heat-dissipation; when heat-production is increased and heat-dissipation remains normal; when both heat-production and heat-dissipation are increased, but when heat-production is increased to a greater extent than heat-dissipation; and when heat-production is increased and heat-dissipation is diminished. The temperature is *diminished* when heat-production is normal and heat-dissipation is increased; when heat-production is diminished and heat-dissipation remains normal; when heat-production and heat-dissipation are diminished, but when heat-production is diminished to a greater extent than heat-dissipation; when heat-production is diminished and heat-dissipation is increased; and when both heat-dissipation and heat-production are increased, but when heat-production is increased to a less extent than heat-dissipation.

It is generally regarded by clinicians that bodily temperature varies directly with heat-production—that is, that a rise means increased production, and a fall diminished production; but the fallaciousness of such a conclusion must be apparent. It may, however, be accepted as a fact that in fever, as a rule, an increase of bodily temperature is a concomitant of increased heat-production, and diminished temperature of diminished heat-production; but it must also be observed that pyrexia, although generally due to increased heat-production, may also be due partly or wholly to diminished heat-dissipation. It is obvious, therefore, that temperature variations simply show that the balance between heat-production and heat-dissipation is disturbed, without positively indicating how the processes of heat-production and heat-dissipation are affected.



The mechanism concerned in the adjustment of the relations between heat-production and heat-dissipation will be considered under another heading (p. 495).

#### B. INCOME AND EXPENDITURE OF HEAT.

Broadly speaking, the source of animal heat is in the potential energy of organic food-stuffs—a little relatively being obtained from the heat of warm food and drink and directly from external sources, such as the sun's rays, but these sources may be disregarded.

The experiments of Rummel have clearly shown that chemical changes in the body constitute the source of animal heat. He made estimations of the amount of heat that should be formed in the body as indicated by the exchange of oxygen and carbon dioxide, and also determined by direct calorimetry (see below) the heat production in dogs under conditions of fasting and varying diet. The results in the two cases are strikingly close, as will be observed from the following table:

Condition of dog.	Quantity of heat calculated.	Quantity of heat obtained by calorimeter.	Percent difference.
Fasting	1162.7 calories	1180.1 calories	-1.42
Food: hay	1201.2 "	1205.3 "	-0.97
"    "    "    "    "    "    "    "	1208.4 "	1221.2 "	-0.42
"    "    "    "    "    "    "    "	1210.5 "	1224.1 "	-0.43

These figures, which are so close, indeed, are substantiated in their correctness and import by the results obtained by Lillig and Lillig in studies on guinea-pigs, rabbits, chicks, and dogs.

This potential energy of food may be converted into heat *directly or indirectly*: directly, as an immediate result of chemical decomposition; and indirectly, by mechanical movements, such as muscular contraction, the flow of the blood, the friction of the organs, etc. About 90 per cent. of the heat of the organism results directly from chemical decompositions, and about 10 per cent. results indirectly from mechanical movements. The potential energy of the food is transformed into kinetic energy (heat and work) essentially by processes of oxidation. The energy-yielding food-stuffs enter the body in the form of solids, liquids, and gaseous states. The protein is broken up into urea,  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ , and various fatty acids; and the fats and carbohydrates into  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . During these oxidative processes, by which the potential energy of the molecules is transformed into kinetic energy, the total amount of energy evolved by the complete oxidation of a given amount of any substance is the same whether the processes are carried at once to the final stages, that is, to the final decomposition products, or whether they pass through an indefinite number of intermediate stages, provided that the final product or products are the same. In other words, the amount of heat evolved by the oxidation of 1 gram of protein into urea,  $\text{CO}_2$ , and  $\text{H}_2\text{O}$  is the same when the molecule is oxidized immediately into these substances as when the decomposition is carried through a number of intermediate stages.

*Journal of Biology*, 1903, Bd. III, p. 72.      *Journal of Neurology*, 1898, p. 743.

**Income of Heat.**—Since the energy-yielding food-stuffs are essentially proteids, fats, and carbohydrates, and composed of C, H, O, and N, and since the products of their disintegration are essentially urea,  $\text{CO}_2$ , and  $\text{H}_2\text{O}$ , the amount of energy yielded by the oxidation of the food-stuffs can readily be determined if we know the quantity and quality of the food and excreta. Since the energy of the organism is manifested essentially in the form of heat and work, and as under ordinary circumstances but a fraction of it is manifested as work, we may in making this estimate, as a matter of convenience, consider that the total available energy of the food appears in the form of heat.

The income of energy has been estimated by determining—(1) the quantity of oxygen consumed; (2) the amounts of C and H that are oxidized in the body into  $\text{CO}_2$  and  $\text{H}_2\text{O}$ ; (3) the quantity and quality of the food consumed in the body and the products resulting from their decomposition, and the energy yielded by the oxidation of the same substances outside the body when they are decomposed into the same residual products as appear in the body; (4) the quantity of heat produced, by the aid of a calorimeter, the individual being kept quiet so that as little as possible of the energy expended appears as work. The third method is a method of *indirect* calorimetry, and the fourth method that of *direct* calorimetry, or, briefly, calorimetry.

The first two methods have fallen into disuse. According to the third method, it is necessary that we know the kind and quantity of food consumed, the final products of disintegration, and the quantity of energy evolved by the conversion of each of the food-stuffs to its normal residual substances. As the basis of these calculations we have the fact that during the complete oxidation of any given substance a definite amount of energy is given off, and that when the oxidation is but partial only a portion of energy is evolved, the proportion being in accordance with the stage of oxidation. The complete oxidation of 1 gram of proteid yields 5778 calories; of 1 gram of fat, 9312 calories; and of 1 gram of carbohydrate, 4116 calories (see *Potential Energy of Food*, p. 364). If these substances be completely oxidized in the body, the amount of energy evolved will be the same as though the oxidation occurred outside of the body, provided that the final products are the same in both cases. As far as fats and carbohydrates are concerned, we are justified in assuming that they are completely oxidized in the body into  $\text{CO}_2$  and  $\text{H}_2\text{O}$ ; but the proteids, as already pointed out, undergo only partial oxidation, each gram yielding about one-third of a gram of urea. The results of experiments show that each gram of urea contains potential energy equivalent to 2523 calories, and since each gram of proteid yields one-third of a gram of urea, representing 841 calories, each gram of proteid yields theoretically to the organism only 4937 calories. The available energy from the proteid would, therefore, be equivalent to the total amount of energy derivable from the complete oxidation of the proteid minus the amount represented in the urea. Practically,



according to the experiments of Rubner, each gram of proteid is estimated to yield 4100 calories. With these facts in view it is a simple matter to determine the total income of energy, should the diet be known. Thus, if the diet consists of 120 grams of proteids, 90 grams of fat, and 330 of carbohydrates, the absolute and available amounts of energy ingested are—

	Grams.		Calories.	Calories.
Proteids . . . . .	120	×	5778	693,360
Fats . . . . .	90	×	9312	837,080
Carbohydrates . . . . .	330	×	4116	1,358,280
				2,888,720
Deduct the proteid energy in 40 grams of urea, $40 \times 2523 =$				100,920
Total daily heat-production . . . . .				2,787,800

This is assuming that the entire quantity of proteids, fats, and carbohydrates is digested, absorbed and ultimately broken down into  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ , and urea. This assumption, however, is not justified by facts, since we know, for instance, that more or less food escapes digestion. Moreover, the calorimetrical values, at least for proteids, are probably too high. In practice, therefore, it is necessary to ascertain from the excreta of the animal (see section on Nutrition) just how much of the ingested food has been absorbed and completely or partially destroyed in the body.

Calorimetric investigations also afford us indirect information as to the *income* of heat by showing the quantities of heat produced and dissipated. Such data are of much value, since it is evident that should the energy of the body be maintained in a condition of equilibrium from day to day, and should the energy resulting from the transformation of potential energy be manifested solely in the form of heat, it follows that the mean daily heat-production and income of available energy must balance. But it cannot be considered that this balance is maintained at a constant standard from hour to hour, nor from day to day; on the contrary, the fluctuations are undoubtedly considerable, as is obvious by the fact that we are continually expending energy and only periodically (at meal-times) acquiring energy. During fasting there is absolutely no income of energy, yet the output of heat may be subnormal, normal, or hypernormal; on the other hand, if an excess of energy be ingested, as in excessive eating, it is not by any means implied that there is a similar excess in heat-production, because some of the food ingested may be lost as undigested food or as partially oxidized excrementitious matters, or may be stored in the body in the form of carbohydrate, fat, or proteid; nor does an excess of heat-production imply an excess of income of energy, because the stored-up energy may be drawn upon. (For results of the calorimetric method see p. 482.) The results of the various methods are in close accord, and indicate that in the adult the total income of available energy is about 2,500,000 calories.

**Expenditure of Heat.**—Assuming that the energy of the organism is expended in the form of heat, and that the total income of available energy is 2,500,000 calories, it has been estimated by Vierordt that about—

1.8 per cent. is lost in the urine and feces . . . . .	47,500 calories.
3.5 " " " expired air . . . . .	84,500 "
7.2 " " " evaporation of water from the lungs . . . . .	182,120 "
14.5 " " " " " " skin. . . . .	364,120 "
73.0 " " " radiation and conduction from skin . . . . .	1,791,820 "
	2,500,000 calories.

Therefore, about 87.5 per cent. is lost by the skin, 10.7 per cent. by the lungs, and 1.8 per cent. in the urine and feces.

### C. HEAT-PRODUCTION AND HEAT-DISSIPATION.

**Calorimetry.**—The *intensity* of heat of any substance is measured by means of a thermometer or thermopile; the *quantity* of heat present is estimated by the weight, the specific heat, and the mean temperature of the body; the quantity of heat *dissipated* is measured by the calorimeter; and the quantity of heat *produced* is determined by the quantity dissipated plus any addition of heat to that of the body or minus any that is lost (p. 481). The *caloric*, or heat unit, is the quantity of heat that is necessary to raise the temperature of one gram of water 1° C.; the mechanical unit, or *grammeter*, is the quantity of energy required to raise one gram a height of one meter, 424.5 grammers being equal to 1 caloric; a *kilocaloric* or *kilogramdegree* is equal to 1000 calories, and a *kilogrammeter* to 1000 grammers. By *specific heat* is meant the quantity of heat required to raise the temperature of any substance 1° C., this quantity varying considerably for different substances. If water be taken as 1, as a standard of comparison, the specific heat of the animal body may be regarded as being about 0.8; in other words, 0.8 of the quantity of heat will be required to heat the animal body as to heat the same weight of water. Knowing the weight, specific heat, and temperature of any substance the total quantity of heat stored in it at a given temperature, compared with the same body at 0° C. may be readily calculated. Thus, if the animal experimented upon weigh 20 kilos, its specific heat be 0.8, and its temperature be 39°, the total quantity of heat stored would be  $20 \times 0.8 \times 39 = 62.4$  kilogramdegrees. In calorimetric work the total heat in the organism is seldom considered, but the specific heat of the organism is of importance in determining the quantity of heat involved in a change of the animal's temperature. For instance, should the animal weigh 20 kilograms and its temperature be increased or decreased 0.2°, the quantity of heat added to or taken from the heat of the body, as the case may be, would be  $20 \times 0.8 \times 0.2 = 3.20$  kilogramdegrees. These calculations are of fundamental importance in studying heat-production and heat-dissipation.

In making estimates of the dissipation of heat no regard is paid usually to the quantity lost in the urine and feces, because the error involved is so slight, but the quantities imparted to the air, both in warming the inspired air and in evaporating water from the lungs and skin, represent important percentages.

Calorimetry is spoken of as direct and indirect. The former method is the direct determination of the amount of heat produced and dissipated; the



latter is the indirect determination based upon estimates of the quantities of O absorbed and CO<sub>2</sub> eliminated, or upon the amount of potential energy ingested in the food and probably transformed into kinetic energy within the body (p. 474).

Calorimeters of various forms have been employed, some of which have been devised to study the body as a whole, while others are adapted only for studying parts, such as a leg or arm. They may be classified as *ice*, *air*, and *water* calorimeters in accordance with the chief medium employed to absorb the heat. They consist essentially of an insulated jacket of ice, air, or water, which encloses the animal and serves to absorb the heat. The ice calorimeter is impracticable for physiological uses; the air calorimeter until very recent years has found but little acceptance, but is deservedly fast gaining in popularity; the water calorimeter is the form of apparatus usually employed, having been first used by Crawford in 1788; it has been materially modified by Despretz and Dulong and subsequent investigators. The now classical instrument of Dulong consists of two concentric cases. The animal is placed within the smaller case, which is submerged in the water contained in the larger case, this in turn being placed within a large box, between which and the calorimeter some non-conducting material such as feathers or wool is packed. Suitable openings are made for the proper supply of fresh air and for the agitation of the water in the calorimeter so that an equalization of the temperature of the instrument can be obtained. This apparatus has certain serious defects, however, which render it troublesome for expeditious and accurate work. An improved form devised by the author<sup>1</sup> which is now in general use meets every essential requirement for a satisfactory instrument. The apparatus consists of two concentric boxes of sheet metal which are fastened together so that there is space of about one and a half inches between them filled with water (Fig. 80). The outer box is fifteen inches in height and width, and eighteen inches in length. An opening (*h*) nine inches in diameter is made in one end for the entrance and exit of the animal. It is also perforated with three small holes in the top corners, and a slit-like opening in the top on one side. Two of the holes are for the tubes for the entrance and exit of air (*EN*, *EX*), the entrance tube being carried close to the bottom, while the exit tube extends only to the top of the box, and is placed in the opposite diagonal corner, thus ensuring adequate ventilation. In the third hole a thermometer (*CT*) is inserted, by means of which the temperature of the calorimeter (jacket of metal and water) is obtained. The opening in the side is for the insertion of a stirrer (*S*), which is for the purpose of thoroughly mixing the water and thus equalizing the temperature of both water and metal—in other words, of the calorimeter.

Before using the apparatus the *calorimetric equivalent* must be determined, that is, the amount of heat required to raise the temperature of the instrument 1°. This may be obtained indirectly by knowing the different substances used in the construction of the instrument, their weights, and their specific heats, and estimating from these data. It is better, however, to make the determination

<sup>1</sup> Reichert: *University Medical Magazine*, 1890, vol. 2, p. 173.

by burning a definite amount of absolute alcohol or hydrogen within the instrument, or by using a sealed vessel of hot water of a known temperature and allowing it to cool to a definite extent. The process is simple; for instance, each gram of alcohol or each liter of hydrogen completely oxidized yields a definite number of calories; similarly, a definite weight of water cooled a

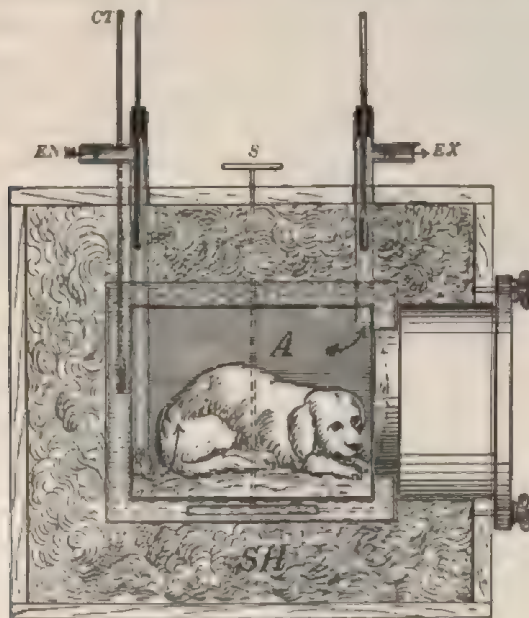


FIG. 80.—Reichert's water calorimeter.

definite number of degrees gives off a definite quantity of heat. The heat thus generated by the oxidation of the alcohol or hydrogen or given off by the cooling of the water is imparted to the calorimeter and increases its temperature. Knowing the quantity of heat given to the calorimeter and the increase of temperature of the instrument, the determination of the calorimetric equivalent may be easily made. Thus, 1 gram of alcohol yields in round numbers 7000 calories; if we burn 10 grams of absolute alcohol, 70,000 calories will result; if the temperature of the calorimeter be increased  $1^{\circ}$ , the calorimetric equivalent will be 70,000 calories or 70 kilogramdegrees; in other words, for each degree of increase of the temperature of the calorimeter a quantity of heat equivalent to 70 kilogramdegrees is absorbed.

The heat dissipated by an animal is only in part absorbed by the calorimeter, another portion being given to the air which passes from the instrument, and another portion to water which is evaporated from the lungs and skin. Three estimates, therefore, are necessary—(1) of the heat given to the calorimeter, (2) of the heat given to the air, and (3) of the heat given off in the evaporation of water.

The estimate of the heat given to the air necessitates the measurement of the quantity of air supplied to the calorimeter, and of the temperature of the



air on entering and leaving the calorimeter; while the estimate of the heat lost in evaporating water involves the measurement of samples of the air entering and leaving the instrument and of the quantities of water in both cases, the total quantity of water evaporated from the animal being estimated from these data.

The conduct of such experiments is not attended with any material difficulties. The water of the calorimeter is stirred for a sufficient length of time in order to obtain a uniform temperature. The temperature of the animal is taken and the animal then placed within the animal chamber. The temperatures of the calorimeter and of the air entering and leaving the instrument, and readings of the three gas-meters are recorded. During the progress of the experiment air temperatures are recorded at regular intervals of ten or fifteen minutes and the water stirred for a few seconds each time. At the conclusion of the experiment there are recorded—the temperature of the calorimeter, the temperatures of the air entering and leaving the calorimeter, the quantities of air passing through the three gas-meters, and the temperature of the animal.

The quantity of heat given to the *calorimeter* is now determined by multiplying the increase of temperature of the instrument by the calorimetric equivalent. If the rise of temperature be  $0.6^{\circ}$  C. and the calorimetric equivalent be 90 kilogramdegrees, the quantity of heat imparted to the water jacket will be  $90 \times 0.6^{\circ} = 54$  kilogramdegrees.

The quantity of heat imparted to the *air* is determined by finding first the corrected volume of the air, then reducing the corrected volume to weight, then multiplying the weight by the specific heat of air at  $0^{\circ}$  C., and finally multiplying by the increase of temperature. The corrected volume may be

obtained by the following formula:  $V = \frac{V' P}{760 (1 + 0.003665 t)}$ , where  $V$  is

the required volume at  $0^{\circ}$  C. and 760 mm. barometric pressure,  $V'$  the observed volume,  $P$  the observed pressure, and  $t$  the observed mean temperature:  $760 (1 + 0.003665)$  is conveniently obtained from standard tables. The errors incident to changes in barometric pressure and in aqueous tension are so slight that they are not usually taken into consideration. Assuming that the quantity of air supplied amounted to 6000 liters, and that the mean temperature of the air was  $20^{\circ}$ , the corrected volume would be, omitting barometric

pressure and aqueous tension,  $V = \frac{V' P}{(1 + 0.003665 t)} = \frac{6000}{1.0733} = 5590$  liters

at  $0^{\circ}$  C. One liter of dry air at  $0^{\circ}$  C. weighs 0.001293 kilogram; therefore,  $5590 \text{ liters} \times 0.001293 = 7.228$  kilograms. If we assume that the air during its passage through the calorimeter had its temperature increased  $3^{\circ}$ , and the specific heat of air is 0.2377, the quantity of heat imparted to the air must have been  $7.228 \times 3 \times 0.2377 = 5.152$  kilogramdegrees.

The next estimate is of the quantity of heat lost in the *evaporation of water*. This is determined by finding the difference between the quantities

of water in the samples of the air passing into and from the calorimeter, and estimating from these results the amount of moisture imparted to the total air leaving the chamber. Assuming that 10 grams of water were thus evaporated, since each gram requires about 582 calories or 0.582 kilogramdegree, the quantity of heat evolved would be equal to  $10 \times 0.582 = 5.82$  kilogramdegrees.

The total quantity of heat dissipated would therefore be the sum of the quantities given to the calorimeter, to the air, and to the water evaporated:

Given to the calorimeter . . . . .	54,000	kilogramdegrees.
Given to the air . . . . .	5,152	"
Lost in evaporating water . . . . .	5,820	"
Total heat-dissipation . . . . .	64,972	"

The quantity of heat produced is determined by adding to or subtracting from the quantity dissipated the amount of heat that may have been gained or lost by the organism. It is obvious that any difference between the quantities of heat dissipated and produced must be represented by an increase or decrease of the mean temperature of the animal. If the animal's temperature remains unchanged, the quantity of heat produced is the same as the quantity lost; if, however, the animal's temperature increases, less heat is dissipated than is produced; if it falls, *vice versa*. The quantity of heat involved in a change of body-temperature is determined by the product of the change in temperature into the animal's weight and specific heat. Assuming that the animal's temperature at the beginning of the experiment was  $38.95^{\circ}$  C. and at the end  $39.32^{\circ}$  C., the temperature being increased  $0.37^{\circ}$  C., that the animal's weight was 25 kilograms, and that the animal's specific heat was 0.8, the quantity of heat would be  $0.37 \times 25 \times 0.8 = 7.4$  kilogramdegrees. The quantity of heat produced would, therefore, be the total quantity dissipated plus the quantity of heat added to the heat of the organism at the time the experiment begun; therefore, the heat-production was  $64.972 + 7.4 = 72.372$  kilogramdegrees. If the animal's temperature had fallen, more heat would have been dissipated than produced, because the total quantity of heat in the organism was greater at the beginning than at the end of the experiment; therefore, the quantity of heat represented in the change of temperature would have been deducted from the quantity of heat dissipated.

While calorimetric experiments do not generally involve any special difficulties, accurate results can only be ensured by the strict observation of certain details: (1) The temperatures of the calorimeter and room should be as nearly as possible alike and kept as far as possible constant. (2) The thermometers employed should be so sensitive that readings can be made in hundredths of a degree, and they should respond very quickly, so that rectal temperatures can be obtained within three minutes. (3) Rectal temperatures are to be preferred, the thermometer always being inserted to the same extent and held in the same position, care being exercised to prevent the burying of the bulb in fecal matter. (4) The animal during the taking of its temperature must on no account be tied down, but gently held, and all circumstances sedulously avoided



that tend to excite the animal. The chief sources of error in the calorimetry are in failures to obtain accurate temperatures of the calorimeter and of the animal. In the latter case inaccuracy is to some extent absolutely unavoidable, chiefly because of normal fluctuations which occur frequently and are often very marked.

**Conditions affecting Heat-production.**—The quantity of heat produced must necessarily vary with many circumstances. Estimates of heat-production in the adult range in round numbers from 2000 to 3000 kilogramdegrees per diem according to the method and incidental circumstances. Thus, according to—

Scharling . . . . .	3169 kilogramdegrees	Ranke . . . . .	2272 kilogramdegrees
Vogel . . . . .	2400 "	Rühlner . . . . .	2843 "
Hirn . . . . .	3725 "	Ott . . . . .	103 "
Leyden . . . . .	2160 "	per hour during the afternoon (weight of man 87.3 kilograms).	
Hemholtz . . . . .	2732 "	Lichatschew . . . . .	33.072 to 38.723 kilo-
Rosenthal . . . . .	2446 "	gramdegrees per kilogram of body-weight	
Danilesky . . . . .	3210 "	per diem. <sup>1</sup>	
Ludwig . . . . .	3192 "		

The chief conditions which affect heat-production are age, sex, constitution, body-weight and body surface, species, respiratory activity, the condition of the circulation, internal and external temperature, food, digestion, time of day, muscular activity, the activity of heat-dissipation, nervous influences, drugs, abnormal and pathological conditions.

*Young* animals produce more heat, weight for weight, than the mature. This is owing chiefly to the greater activity of the metabolic processes in the former, and in part to the relatively larger body surface, young animals generally being smaller than the matured and thus having, in proportion to body-weight, larger radiating surfaces.

Heat-production is more active in the *robust* than in the *weak*, other conditions being the same.

The *weight of the body* is obviously a most important factor in relation to the quantity of heat produced, especially as regards the weight of the active tissues in relation to inactive structures such as bone, sinew, and cartilage. Two animals of the same weight may produce very different quantities of heat per diem, other things being equal. Thus, a fleshy animal should naturally be expected to produce more heat than one with very little flesh and an abundance of fat, which is an inactive heat-producing structure. While, therefore, the relation of heat-production to body-weight does not seem to be definite, yet the experiments by Reichert<sup>2</sup> and by Carter<sup>3</sup> indicate that heat-production bears, broadly speaking, a direct relation to body-weight.

Heat-production is greater relatively in *homothermous* than in *poikilother-*

<sup>1</sup> The figures by Ott (*New York Medical Journal*, 1889, vol. 16, p. 29) and Lichatschew (*Dis. inauguralis*, St. Petersburg, 1893; quoted in Hermann's *Jahresberichte der Physiologie*, 1893, S. 99) were obtained by means of a water calorimeter.

<sup>2</sup> *University Medical Magazine*, 1890, vol. 2, p. 225.

<sup>3</sup> *Journal of Nervous and Mental Diseases*, 1890, vol. 17, p. 782.

*mammals* animals; it varies materially in intensity in *different species*, especially in warm-blooded animals; and it is closely related to the intensity of respiration. Moreover, it is probable that each species, and even each individual of the species, has its own specific thermogenic coefficient, that is, a mean standard of heat-production for each kilogram of body-weight or for each square centimeter of body-surface. The following figures giving the heat-production per kilogram per hour, compiled by Munk,<sup>1</sup> are of interest both as regards species and size and weight of the animal in relation to heat-production:

Horse . . . . .	1.3 kilogramdegrees.	Duck . . . . .	6.0 kilogramdegrees.
Man . . . . .	1.5 "	Pigeon . . . . .	10.1 "
Child (7 kilograms) . .	3.2 "	Rat . . . . .	11.3 "
Dog (30 " ) . .	1.7 "	Mouse . . . . .	19.0 "
Dog (8 " ) . .	3.8 "	Sparrow . . . . .	35.5 "
Guinea-pig . . . . .	7.5 "	Greenfinch . . . . .	35.7 "

These figures have an additional interest when compared with the respiratory activity of different species (p. 429). The intensity of respiration has a marked significance both in connection with the species and the individual. The larger the quantity of oxygen consumed the greater relatively is the activity of oxidation processes, and, consequently, the more active is heat-production (see p. 429). Therefore, all circumstances which affect respiratory activity tend to affect thermogenesis. The intensity of respiratory activity and the extent of body-surface in relation to body-weight are closely related (p. 430).

*Increased activity of the circulation* is favorable to increased heat-production, this being due to several factors: (1) A more abundant supply of blood may be accompanied by increased metabolic activity. (2) Increased circulatory activity is favorable to increased heat-dissipation by causing a larger supply of blood to the skin, thus facilitating loss by radiation and indirectly tending to increase thermogenesis. (3) Increased circulatory activity also excites the respiratory movements and the secretion of sweat, thus increasing heat-loss and indirectly favoring heat-production. (4) The more active the circulation the larger the amount of heat produced by the heart and the movement of the blood. The diurnal fluctuations of the pulse-rate are said to be more or less closely related to similar changes of body temperature.

A rise of *internal temperature* (body temperature) is favorable to increased metabolic activity (p. 432) and, therefore, to an increase of heat-production; conversely, a fall of body temperature tends to reduce heat-production. The influences of body temperature are, as a whole, less important than those of external temperature.

The influences of *external temperature* are in a measure different upon homo-thermous and poikilothermous animals. In the former, heat-production is in inverse relation to the temperature of the surrounding medium, so that the cooler the ambient temperature the greater the heat-production; in the latter

<sup>1</sup> *Physiologie des Menschen und der Säugethiere*, 1892, S. 302.



heat-production increases with an increase of external temperature, because with the rise of the latter bodily temperature increases, which in turn increases metabolic activity (pp. 432, 433). Consequently, in warm-blooded animals heat-production is greater in cold climates and seasons than in the opposite conditions, while in cold-blooded animals the opposite is the case. Cold applied to the skin increases heat-production by reflexly exciting muscular activity (shivering, etc., p. 433); moderate heat exerts the opposite influence unless the bodily temperature is affected, as shown by the results of studies of respiration (p. 433).

The character of the *food* is important. Danilewsky<sup>1</sup> has estimated that the following quantities of heat are produced under different diets, etc.:

On a minimum diet . . . . .	1800 kilogramdegrees.
On a reduced diet (absolute rest) . . . . .	1989 "
On a non-nitrogenous diet . . . . .	2480 "
On a mixed diet (moderate work) . . . . .	3210 "
On an abundant diet (hard work) . . . . .	3646 "
On an abundant diet (very laborious work) . . . . .	3780 "

The influence of the quantity and quality of the diet must be potent when it is remembered that 1 gram of proteid yields about 4100 calories, 1 gram of fat about 9312 calories, and 1 gram of carbohydrate about 4116 calories. In cold climates fats enter very largely into the diet because of the greater loss of heat and the consequent increased demand for heat-producing substances.

During the *periods of digestion* more heat is produced than during the intervals, this increase being due chiefly to the muscular activity of the intestinal walls (p. 431). Langlois' experiments indicate that during digestion heat-production may be increased 35 to 45 per cent.

It is said that heat-production undergoes diurnal variations which correspond with the fluctuations of bodily temperature, but this is doubtful.

All structures produce more heat during *activity* than during rest. Heat-production has been estimated to be from two and a half to three times greater when awake and resting than when asleep, and from one and a half to three times more when active than when at rest, in proportion to the degree of activity. During hybernation the absorption of O falls considerably (p. 434), consequently heat-production is believed to decline to a like degree.

All conditions which affect *heat-dissipation* (p. 494) tend indirectly to influence heat-production.

The most important of the factors influencing heat-production is the *nervous mechanism* which controls the heat-producing processes (p. 490).

Various *drugs* exert more or less potent influences directly or indirectly upon heat-production. Cocain, strychnin, brucin, and other motor excitants increase heat-production; while chloroform, most antipyretics, narcotics generally, bromides, and motor depressants decrease heat-production.

Heat-production is diminished in most forms of anæmia, after severe hemorrhage, and in most non-febrile adynamic conditions. It is usually increased in fevers, especially so in infectious fevers. According to Liebermeister, the

<sup>1</sup> *Pflüger's Archiv für Physiologie*, 1883, Bd. xxx. S. 190.

increase in fever is probably about 6 per cent. for each increase of  $1^{\circ}$  C. of bodily temperature, so that were the increase of temperature  $3^{\circ}$  C. the increase of heat-production would be 18 per cent.

**Conditions affecting Heat-dissipation.**—The loss of heat from the body occurs through several channels—in the urine, feces, sweat, and expired air, and by radiation and conduction from the skin; hence, all conditions which affect the loss of heat in the above ways must influence heat-dissipation. The chief of these are: Age, sex, species, the quantity of subcutaneous fat, the nature of the surrounding medium, clothing, internal and external temperature, activity of heat-production, body-surface, the condition of the circulation, respiration, sweat, activity, radiating coefficient, nervous influences, drugs, and abnormal conditions.

The influence of *age* is shown by the fact that the young dissipate and produce more heat in proportion to body-weight than the adult, this being due chiefly to the relatively greater metabolic activity and the larger proportional body-surface (p. 430), and consequent greater radiation, in the young.

*Sex per se* does not seem to exert any influence, although the adult human female, weight for weight and for an equivalent bodily surface, probably dissipates less heat than the male, because of her relative abundance of subcutaneous fat, which hinders heat-dissipation. No difference so far as sex is concerned has been noted in the lower animals.

Heat-dissipation varies greatly in different *species*, owing chiefly to relative size and respiratory activity, to the nature of the medium in which the animal lives, and to the character of the body-covering. Heat-dissipation is more active in homothermous animals than in poikilothermous animals, because of the greater activity in the former of heat-production. In amphibia heat-dissipation is greater when the animal is in the water than when exposed to the air if both water and air be of the same temperature, because water is a better conductor of heat and consequently withdraws heat from the body more rapidly. The higher the temperature of the surroundings the higher the bodily temperature of cold-blooded animals, consequently the greater are heat-production and heat-dissipation. In warm-blooded animals the effect on both heat-production and heat-dissipation is in inverse relation to the surrounding temperature (unless the bodily temperature is affected), external heat decreasing both heat-dissipation and heat-production, and internal heat increasing both.

*Subcutaneous fat* is a poor conductor of heat, consequently the greater the abundance of it the greater the hindrance offered to the dissipation of heat. The value of fat in this respect is illustrated in water-fowls, which, as a rule, are far more abundantly supplied with fat than other species; and by the exceptional abundance of subcutaneous fat in species of fowl which inhabit very cold waters. Bathing the skin with grease hinders radiation, and is adopted by swimmers both to conserve the bodily heat and to protect the skin.

When air and water are of the same *temperature*, heat-dissipation is greater when the animal is exposed to the water, because the latter is a better conductor. Heat-loss is greater in dry than in moist air, other things being



equal, because in the former the evaporation of sweat from the body and the loss of water from the lungs are favored, the vaporization of water affecting heat-dissipation more decidedly than the moisture of the air. Heat-dissipation is more active in cold moist air than in cold dry air. Cold air is not favorable to the vaporization of water, whereas cold moist air has a higher specific heat than the dry air, and thus tends to carry off heat more rapidly.

The character of the *covering of the body* is of great importance. This is illustrated in the changes which occur in the natural covering of animals during warm and cold seasons, and in the characters of the fur of species which inhabit very cold or very warm climates. During the winter the fur is longer and thicker than during the summer. Animals living in cold or hot climates are supplied with a relatively greater or less abundance of fur or feathers and subcutaneous fat. Man provides for changes of the seasons by modifying the quantity and quality of his clothing. In the adaptation of dress to climate, the conductivity, radiating coefficient, hygroscopic capacity, porosity, weight, and color of the clothing are important factors. The poorest conductors, other things being equal, make the warmest clothing; fur and wool are poor conductors and therefore are adapted especially for cold seasons and climates, while cotton and linen are good conductors and therefore make cool clothing. The radiating coefficient depends upon the conductivity of the material and the character of the radiating surface. The coarser the material the better the radiating surface, hence the better the conductor and the cooler the clothing. The hygroscopic character of the clothing is of far more importance than is generally believed. Articles of clothing having a large capacity for absorbing and retaining moisture are, other things being equal, of more value, especially for underwear, than those possessing the opposite quality. Woollen goods compared with those made of cotton not only have a far greater absorptive capacity but retain moisture for a longer time. When the clothing is of wool people are less apt to catch cold from exposure to draughts and sudden cold than when it is of linen or cotton, the wool preventing a too rapid evaporation of moisture, thus guarding against chilling. Porosity is a comparatively subsidiary factor. The greater the weight of the clothing, other things being equal, the more is heat-dissipation hindered. The color of the outer apparel has a certain influence owing to the relative heat-absorbing capacities, black clothing being warmer than white, etc., hence the general use of white or light-colored clothing in warm climates and seasons.

A rise of *internal temperature* (bodily temperature) is favorable to an increase of heat-dissipation, for several reasons: (1) Heat-production tends to be increased and thus cause an effort of the system to get rid of the excess of heat. (2) The activity of the circulation is increased, causing a larger amount of blood to be brought to the cutaneous surface where it is subjected to the influence of the cooler surroundings. (3) Respiratory movements are increased so that heat-dissipation is favored by the larger amount of air respired and larger amount of moisture carried off. (4) The temperature of the body is higher in relation to that of the surroundings and thus heat-dissipation by

radiation and conduction is facilitated. The influences of external temperature are even more potent in their effects than those of internal temperature, chiefly because of the much wider range of temperature to which the organism is subjected. Bodily temperature under ordinary circumstances does not vary more than  $1^{\circ}$  to  $2^{\circ}$  C. during the twenty-four hours, but external temperature may vary as much as  $40^{\circ}$  C., or more. *External heat* tends by exciting cutaneous nerves to reflexly diminish heat-production and thus indirectly diminish heat-dissipation; but this is to some extent antagonized by a dilatation of the blood-vessels of the skin, an excitation of respiration, and increase in the quantity of sweat, all of which tend to increase heat-dissipation, but which are unable to balance the opposite effects. *Cold*, on the other hand, accelerates both heat-dissipation and heat-production. The loss of heat from the body is increased because of the greater difference in the temperatures of the body and the surroundings; but, on the other hand, the cutaneous vessels are contracted, the circulation is less active, and the quantity of sweat is lessened, all of which are unfavorable to heat-dissipation. Yet while these latter alterations tend to diminish heat-loss, they are not sufficient to compensate for the increased expenditure by radiation and for the greater loss by respiration.

Circumstances which increase *heat-production* above the normal tend indirectly to increase heat-dissipation. Other things being equal, the greater the quantity of heat produced the greater the heat-dissipation, unless the bodily temperature be below the normal, in which case heat-production may be increased and yet heat-dissipation remain unaffected, or even be diminished, until sufficient heat has accumulated to bring the bodily temperature up to the mean standard.

The larger the *surface of the body* exposed to the normally cooler surroundings, the greater is the loss of heat. The larger the animal the greater the body-surface, and therefore the greater is heat-dissipation; but in proportion to body-weight smaller animals have larger body-surfaces, therefore heat-dissipation is *relatively* greater, although not absolutely so (see p. 430). The area of body-surface involved in heat-dissipation is affected by the position of the individual. Thus, by bringing the arms and legs in contact with the body the total surface exposed is lessened. On the other hand, animals which habitually have their legs in apposition with the trunk have their radiating surfaces increased when their legs are extended. For instance, in the rabbit extension of the legs enormously increases heat-dissipation, so that the bodily temperature is profoundly affected.

The condition of the *vascular system* exercises an important influence. Circumstances that excite the circulation affect heat-dissipation both directly and indirectly. Thus, heat-loss is directly increased by the excitation of the respiratory movements, by the increased secretion of sweat, and by the larger supply and increased temperature of the blood to the skin. Increased activity of the circulation also increases heat-production, and thus indirectly affects heat-dissipation. Opposite conditions, of course, lessen heat-dissipation.

The larger the *quantity of air respired*, other things being equal, the larger



the loss of heat by this channel. The heat-loss occurs both in warming the air and in the evaporation of water from the lungs, so that the cooler and drier the air inspired the larger relatively is the heat-loss. The importance of respiration as a heat-dissipating factor is illustrated by the fact that about 10.7 per cent. of the total heat-dissipation occurs in this way (see p. 477).

Next in importance to radiation is the amount of *water evaporated from the skin*. Each gram of water requires 582 calories to vaporize it, and it is estimated (p. 477) that 364,120 calories are dissipated in this way, or 14.5 per cent. of the total heat-dissipation. An increase of external temperature increases the irritability of the sudoriparous glands, thus favoring secretion and heat-dissipation. The value of sweat, however, as a means of carrying off heat, is materially affected by the temperature of the air as well as by the amount of moisture present. The higher the temperature and the less the moisture the more rapidly evaporation occurs, and consequently the greater the loss of heat; when air is moist and of high temperature evaporation takes place relatively slowly, if at all. Therefore, individuals can withstand subjection to dry air of a higher temperature and for a longer period than when the atmosphere is moist. In the former case sweat is rapidly secreted and vaporized, and thus a marked rise of internal temperature may be prevented. James found that a vapor bath at  $44.5^{\circ}\text{C}$ . ( $112^{\circ}\text{F}$ .) was insufferable, while dry air at  $80^{\circ}\text{C}$ . ( $176^{\circ}\text{F}$ .) caused little inconvenience. When air is of high temperature and loaded with moisture we say that it is "sultry," but dry air of the same temperature is not unpleasant.

*Muscular activity* increases heat-production, excites the circulation and respiration, and increases the secretion of sweat, all of which directly or indirectly increase heat-dissipation.

The *surface of the body* as a radiating surface cannot be regarded in the same light as an indifferent, inanimate surface, such as metal or wood. The *coefficient of radiation* (the quantity of heat emitted during a unit of time at a standard temperature from a given area) in an inanimate body remains fixed, because the surface itself is virtually unchangeable; but the coefficient for the living organism is subject to material alterations. These alterations depend chiefly (1) upon the actions of the pilo-motor mechanism whereby the relation of the natural covering (hair or feathers in the lower animals) of the body to the skin is effected; (2) upon changes in the conductivity of the skin owing to variations of the blood-supply; (3) upon the varying thickness of the skin in different species, in different individuals, and in different parts of the body; (4) upon the temperature of the surroundings; (5) upon the extent of the body-surface exposed; (6) upon the character of the clothing. When the arrector pili muscles contract the skin is made tense and the cutaneous blood-vessels are pressed upon and rendered anæmic, thus lessening the quantity of fluid in the skin and as a consequence lowering the coefficient of dissipation; moreover, in animals whose natural covering is fur or feathers, these fibres cause an erection of one or the other, as the case may be, and in this way affect the radiating coefficient. The coefficient is enormously increased by

removing the natural covering, such as the fur of the rabbit, under which circumstances, even though the animal be subjected to a relatively high external temperature, heat-dissipation is so enormously increased that death ensues within two or three days. When one side of the body of a horse was shaved and the animal subjected to an atmosphere having a temperature of  $0^{\circ}\text{C}$ ., the temperature of the skin of the shaven side fell  $8^{\circ}$  in forty minutes, while the temperature of the unshaven side fell only  $0.5^{\circ}$ .

The coefficient is diminished where there is excessive sebaceous secretion, and where grease is artificially applied, and by an accumulation of subcutaneous fat; it is increased by wetting the skin, as by sweat or bathing; and it is affected by many other circumstances.

Through the operations of the *nervous system* heat-dissipation may be affected directly or indirectly by action upon the heat-dissipating and heat-producing processes—circulation, respiration, sudorific and sebaceous glands, and arrector pili muscles.

There are many *drugs* which directly or indirectly affect heat-dissipation. Drugs which cause dilatation of the cutaneous vessels tend to increase heat-dissipation; conversely, those which cause contraction of the blood-vessels hinder dissipation. Diaphoretics increase heat-loss essentially by increasing the amount of sweat. Respiratory excitants increase the loss of heat by means of the increased volume of air respired. Drugs which increase heat-production tend to indirectly increase heat-dissipation.

All *pathological states* which affect heat-production tend to similarly disturb heat-dissipation. Conditions of malnutrition favor heat-dissipation by causing a loss of subcutaneous fat, but this is to a greater or less extent compensated for by the enfeeblement of the circulation, respiration, and metabolic processes in general. In *fever*, both heat-production and heat-dissipation are generally increased, the former being affected more than the latter, so that the bodily temperature rises. In some forms of fever the rise of temperature is essentially due to diminished heat-dissipation.

#### D. THE HEAT-MECHANISM.

The heat-mechanism consists of two fundamental parts, one being concerned in heat-production, and the other in heat-dissipation. Heat-production is briefly expressed as *thermogenesis*; and heat-dissipation, as *thermolysis*. The operations of these mechanisms are so intimately related that fluctuations in the activity of one are rapidly compensated for by reciprocal changes in the other, so that under normal conditions heat-production and heat-dissipation so nearly balance that the mean bodily temperature is maintained within narrow limits.

The regulation of the relations between heat-production and heat-dissipation is termed *thermotaxis*, which regulation may be effected by alterations in either thermogenesis or thermolysis.

**The Mechanism concerned in Thermogenesis.**—The portion of the heat-mechanism concerned in heat-production consists of (1) thermogenic tissues, (2) thermogenic nerves, and (3) thermogenic centres.



*The Thermogenic Tissues.*—Almost if not every tissue of the body may be regarded as being a heat-producing structure. The very fact that oxidative processes lie at the bottom of all forms of vital activity, and that heat-production is a concomitant of oxidation, leads inevitably to the conclusion that as long as cells possess life they must produce heat. There are, however, certain of the bodily structures, especially the skeletal muscles and the glands, which are exceptionally active as heat-producers. Indeed, in the case of the skeletal muscles the heat-producing processes are of such a character as to justify the belief that with them thermogenesis is a specific function, because heat is produced not merely as an incidental product of activity but as a specific product. When a muscle contracts, heat is evolved as an incident of the performance of work, and when it is at rest heat is produced not only as an incident of growth and repair but as the result of a specific act. This latter is proved by the fact that when the muscles have been in a state of prolonged rest, when the chemical changes concerned in growth and in repair of waste are practically inactive, heat-production continues to a marked degree. Moreover, the quantity which is produced varies with the immediate needs of the economy and bears a reciprocal relationship to the quantity of heat formed in other structures,<sup>1</sup> and is regulated apparently by specific nerve-centres.

When the muscles are contracting less than one-fifth of the energy appears as work, and more than four-fifths as heat. The contractions of the heart also furnish an appreciable percentage of heat as an accompaniment of contraction; and considerable heat is formed indirectly by the resistance offered by the blood-vessel walls to the blood current. Indeed, the entire work of the heart becomes converted into heat, representing approximately 5 to 10 per cent. of the total heat-production. The quantity formed as by-products of the activity of various structures during a state of muscular quiet is doubtless small compared with the quantity produced by the muscles.

*The Thermogenic Nerves and Centres.*—Heat-production may occur independently of, but under normal circumstances it is regulated by, the nervous system. A muscle separated from all nervous influences continues to produce heat, but considerably less than before, and it ceases to respond to the demands of the system for more or less heat as do muscles with their nerves intact. Injuries to certain parts of the cerebro-spinal axis affect heat-production in muscles, in some instances causing an increase and in others a decrease; but these changes do not occur if the nervous communication between the centres and muscles is destroyed.

*Thermogenic Nerves.*—Specific thermogenic nerve-fibres have not as yet been isolated, although the researches of Kemp,<sup>2</sup> Reichert,<sup>3</sup> Schultz,<sup>4</sup> and others indicate that such fibres exist. In the skeletal muscles probably three independent kinds of processes go on which produce heat, one subservient to the contractions of the muscles, as observed in locomotion, etc.;

<sup>1</sup> Rübner: *Sitzungsberichte d. k. Bayer. Akad. der Wissenschaft*, 1885, Heft 4.

<sup>2</sup> *Therapeutic Gazette*, 1889, p. 155.

<sup>3</sup> *Ibid.*, 1891, p. 151.

<sup>4</sup> Schultz: *Archiv für experimentelle Pathologie und Pharmacologie*, 1899, Bd. 43, S. 193.

another in the form of contraction known as shivering; and a third, giving rise to heat as the only important phenomenon. The heat produced by muscles in ordinary or general muscular acts and in repair and growth is a mere incident to activity; but the heat arising during shivering is undoubtedly a specific product—*i. e.*, the object of the shivering is a production of heat (see p. 433). If the nerve-fibres which convey the impulses that cause shivering be ordinary motor fibres, then these fibres are not only motor fibres, but specific thermogenic fibres in so far as they are connected with heat-production by this act. There are also, apparently, fibres which are entirely distinct from the motor fibres, and which convey impulses that give rise to heat-production as a specific product, and even in the entire absence of motor phenomena. Thus, in a curarized animal in which all motor activity of the skeletal muscles is abolished, an enormous increase of heat-production may occur (Reichert) which cannot satisfactorily be explained in any other way than by assuming the existence of such specific thermogenic fibres. Our information at present is, however, so limited that we can do scarcely more than speculate.

Our knowledge of the character of the afferent fibres which carry impulses that reflexly affect thermogenesis is very unsatisfactory. There can be no doubt that sensory impulses arise in various parts of the organism, especially in the skin, which exercise important influences upon the heat-producing processes. Thus, cooling the skin reflexly excites heat-production, which cannot be attributed to indirect influences upon other functions, but whether or not there exist specific afferent thermogenic fibres is not known. It is possible that the temperature nerves of the skin, the cold and the heat nerves, may be responsible for reflex excitation or depression of heat-production.

*The Thermogenic Centres.*—The existence of specific thermogenic centres has for many years been conceded, but it has only been recently that hypothesis has given place to fact. The most important results of recent research may be generalized as follows: (1) That the irritation of the skin by heat or cold is followed by marked changes in thermogenesis, which effects are to a certain extent entirely independent of vasomotor and other incidental changes, and which, therefore, are due in part to an increase of heat-production dependent directly upon efferent thermogenic impulses. (2) That injury or excitation of certain parts of the brain is followed by an increase of heat-production. (3) That injury or excitation of certain other parts of the brain is followed by diminished heat-production. (4) That injury of the spinal cord may be followed by an increase or decrease of heat-production which cannot be entirely accounted for by vaso-motor and other attendant alterations. (5) That after operations upon certain parts of the cerebro-spinal axis there follows an increase or decrease in the quantity of  $\text{CO}_2$  formed, indicating a corresponding effect on the heat-producing processes.

The results of recent calorimetric work show that there are definite regions of the cerebro-spinal axis which are apparently specifically concerned in thermogenesis; that the effects of excitation or destruction of each region are more



or less characteristic; and that the different regions seem to be so intimately related to one another as to constitute a co-ordinate mechanism. Certain of these regions when irritated give rise, as a direct result, to increased thermogenesis, hence they are of the nature of *thermo-accelerator* centres; and others to diminished thermogenesis, hence are *thermo-inhibitory* centres. Both kinds of centres seem to be associated with and to govern a third kind which is distinguished as the *general* or *automatic* thermogenic centres. The mechanism may be theoretically expressed in this form: The general thermogenic centres may be regarded as maintaining by virtue of independent activity a fairly constant standard of thermogenesis, and as being influenced to increased activity by the thermo-accelerator centres and to diminished activity by the thermo-inhibitory centres. The finer or smaller variations in thermogenesis are presumably effected by the general centres, whereas the grosser variations are probably effected by the influences of the thermo-accelerator and thermo-inhibitory centres.

Specific heat-centres (thermogenic and thermolytic) have by various observers been held to exist in certain regions of the brain cortex, in the base of the brain just in front of and beneath the corpus striatum, in the corpus striatum, in the septum lucidum and the tuber cinereum, in the optic thalamus, in the corpora quadrigemina, in the pons and medulla oblongata, and in the spinal cord. Some of these centres have been regarded as being thermogenic and others as being thermolytic. Many errors in deduction have, however, been made because of the many inherent difficulties attending experimentation upon the cerebro-spinal axis, and because almost all the methods used necessarily involve injury or excitation of contiguous parts. The methods adopted of studying these various regions have been chiefly destruction or injury by means of a probe, actual cautery, excision, and the injection of cauterants; by transverse incisions across the cerebro-spinal axis so as to separate higher from lower portions of the cerebro-spinal axis; and by excitation by small punctures, electricity, etc.

In classifying these centres we are governed by the results which follow excitation and destruction. When irritation or destruction directly affects thermogenesis, the centre is regarded as being thermogenic, but if heat-dissipation is the process directly affected, the centre is regarded as being thermolytic. In classifying thermogenic centres we would regard the centre as being a general thermogenic centre if it is capable, after the destruction of other thermogenic centres, of causing the normal output of heat; a thermo-accelerator centre is distinguished by the fact that excitation increases thermogenesis, while destruction does not diminish thermogenesis, unless the centre happens to be active at the time, and further by the fact that after its destruction the normal output of heat may continue; a thermo-inhibitory centre is distinguished by a decrease of heat-production following stimulation and by the absence of any permanent effect on thermogenesis when the centre is destroyed. The general or reflex thermogenic centres are undoubtedly continuously active, the degree of activity varying according to the immediate demands of the organism for heat; while the thermo-accelerator and thermo-inhibitory centres are prob-

ably only intermittently active, coming into play when the general centres are of themselves unable to effect a sufficiently rapid compensation.

While it must be admitted that our knowledge of the precise locations, physiological peculiarities, and correlations of the thermogenic centres is by no means complete, we have at our disposal some most important and significant data. The general thermogenic centres have been shown by Reichert<sup>1</sup> to be located in the spinal cord. The thermogenic centres in the brain are either thermo-accelerator or thermo-inhibitory. Thermo-accelerator centres probably exist in the caudate nuclei (possibly also in the tuber cinereum and optic thalami), pons, and medulla oblongata.<sup>2</sup>

Excitation of any one of these regions is followed by a pronounced rise of heat-production; destruction of any one region may or may not be followed by a decrease of heat-production, and if a decrease does occur it may in most cases be attributed to incidental causes, such as shock and other attendant conditions. The centre which is common to the pons and medulla is for the most part probably located in the latter, but it is not so powerful in its influences on thermogenesis as the thermo-accelerator centres in the basal regions of the cerebrum. These cerebral centres are affected by agents which have little or no effect on the heat centres of the spinal cord. Thermo-inhibitory centres have been located in the dog in the region of the sulcus cruciatus and at the junction of the supra-sylvian and post-sylvian fissures.<sup>3</sup> Irritation of either of them is followed by a decrease of heat-production, while their destruction may be followed by a transient increase of heat-production. The cruciate centre is the more powerful. None of these cerebral centres exercises any influence on thermogenesis after section of the spinal cord at its junction with the medulla oblongata.

Theoretically, these centres are associated in this way: The general thermogenic centres are in the spinal cord, and while they are perhaps impressionable to impulses coming to them through various sensory nerves, they are not apparently in the least influenced by cutaneous impulses caused by changes in external temperature nor by changes of the temperature of the blood. It is not improbable that these centres are in the anterior cornua of the spinal cord. The thermo-accelerator and thermo-inhibitory centres are connected with the general centres by nerve-fibres, the former influencing the general centres to increased activity, and the latter to diminished activity. The thermo-accel-

<sup>1</sup> *University Medical Magazine*, 1894, vol. v. p. 406.

<sup>2</sup> Reichert: *University Medical Magazine*, 1894, vol. 6, p. 303. Ott: *Journal of Nervous and Mental Diseases*, 1884, vol. 11, p. 141; 1887, vol. 14, p. 154; 1888, vol. 15, p. 85; *Therapeutic Gazette*, 1887, p. 592; *Fever, Thermotaxia, and Calorimetry*, 1889. Aronsohn and Sachs: *Pflüger's Archiv für Physiologie*, 1885, Bd. 37, S. 232. Girard: *Archives de Physiologie normale et pathologique*, 1886, t. 8, p. 281. Baginsky und Lehmann: *Virchow's Archiv für Physiologie*, 1886, Bd. 106, S. 258. White: *Journal of Physiology*, 1890, vol. 11, p. 1; 1891, vol. 12, p. 233. Baculo: *Centri termici*, 1890, 1891, and 1892. Tangl: *Pflüger's Archiv für Physiologie*, 1895, Bd. 68, S. 559. Schultze: *Archiv für experimentelle Pathologie und Pharmacologie*, 1890, Bd. 43, S. 193.

<sup>3</sup> Wood: "Fever," *Smithsonian Contributions to Knowledge*, 1880, No. 357. Ott: *Journal of Nervous and Mental Diseases*, 1888.



erator and thermo-inhibitory centres seem to be especially affected by cutaneous impulses which are generated by changes in external temperature, and to be influenced by alterations of the temperature of the blood. It is doubtless through these centres that changes in external and internal temperature are able to affect the heat-producing processes. Presumably both an increase of temperature of the blood and cutaneous impulses generated by an increase of external temperature excite the thermo-inhibitory centres, and thus inhibitory impulses are sent to the general centres, lessening their activity; on the other hand, both a fall of temperature of the blood and cutaneous impulses generated by cold presumably excite the thermo-accelerator centres and thus cause impulses to be sent to the general centres, exciting them to greater activity.

**The Mechanism concerned in Thermolysis.**—The loss of heat by the body is in a large measure incidental to attendant conditions and is not a reflex result of the activity of a thermolytic mechanism; in other words, the loss occurs essentially by virtue of the same conditions as would cause inanimate bodies to lose heat. The living homothermous organism differs as regards the loss of heat from dead matter, chiefly in that the rapidity with which heat-dissipation occurs is regulated to a material extent by vital processes. The regulation of the loss of heat is effected by the operations of a complex mechanism—that is, one consisting of a number of distinct although correlated parts. A study of this mechanism, which is designated the thermolytic mechanism, includes a consideration of all of the processes by which heat is lost, of the nervous mechanisms which govern them, and of the conditions which affect them, but especially of those processes and mechanisms which act reciprocally in conjunction with the thermogenic mechanism to maintain the mean bodily temperature. Practically all of the heat lost by the organism occurs by radiation and conduction from the skin, by the evaporation of water from the skin and lungs, and in warming the food, drink, and inspired air. From these facts we believe that mechanisms which affect the blood-supply to the skin, the quantity of sweat secreted, the condition of the surface of the skin, and the quantity of air inspired must in a large measure regulate thermolysis. For instance, if the temperature of the organism be materially increased there occur increased activity of the heart, peripheral vascular dilatation, increased respiratory activity, and (except in fever) an increase in the secretion of sweat. The increase of the activity of the heart together with the dilatation of the cutaneous blood-vessels increases the quantity of blood supplied to the skin; the cutaneous blood-vessels are dilated, exposing a larger surface of blood to the cooler external surroundings, and thus materially favoring the loss of heat by radiation; the increase in the quantity of sweat is favorable to an increase in the amount of water evaporated, and thus to a larger loss of heat in this way; an increase of respiratory activity means a larger volume of air respired, a greater expenditure of heat in warming the air and in the evaporation of water from the lungs. In man the pilo-motor mechanism plays a subsidiary and unimportant part in the regulation of heat-dissipation, but in some lower animals, as in certain birds, it is of considerable importance. The thermolytic mechanism therefore includes the cardiac, vaso-

motor, respiratory, sweat, and pilo-motor mechanisms. All these are affected directly or indirectly by the temperature of the blood and skin. An increase in the temperature of the blood and skin excites all of them so that changes are brought about which favor heat-loss. The respiratory movements especially may be rendered intensely active, and in certain animals to such a marked degree that they may become more frequent than the heart-beats.

*Thermotaxis.*—Thermotaxis or heat-regulation is effected by reciprocal changes in heat-production and heat-dissipation brought about by the intervention of the thermogenic and thermolytic centres, just as the regulation of arterial pressure is effected by the reciprocal relations of the cardiac and vaso-motor mechanisms. If heat-production is more active than heat-dissipation, thermolysis is so affected that the heat-loss is increased, and thus the mean bodily temperature maintained; if heat-production is subnormal, heat-dissipation also falls. Similarly, if heat-dissipation is increased, the heat-producing processes are excited to greater activity to make up the loss; conversely, if heat-dissipation is decreased, heat-production also tends to be decreased. These reciprocal actions depend essentially or wholly upon the influence of cutaneous impulses and the temperature of the blood. For instance, an increase of the temperature of the blood increases the activity of the thermolytic processes, thus effecting a compensation. If we subject an animal to a moderately cold atmosphere, as in the winter, heat-dissipation is increased, but cutaneous impulses are generated which excite the thermogenic centres so that heat-production is also increased, and thus the bodily temperature is maintained practically unaffected. It is only under abnormal conditions or under conditions of intense muscular activity that this reciprocal relationship is so disturbed that changes in one process are not quickly compensated for by changes in the other.

Thermotaxis is effected in a large measure reflexly, especially by *cutaneous impulses* generated by external cold and heat, both thermogenic and thermolytic processes being affected. Cold applied temporarily, as in the form of a douche, bath, sponging, etc., causes constriction of the cutaneous capillaries. This lessens both the quantity and temperature of the blood passing through the skin, the effect of which tends to decrease the dissipation of heat by radiation and conduction. Moreover, a lessened blood-supply causes the skin to become poorer in fluid, so that the conduction of heat from the warmer inner parts is lessened. The conductivity of the skin is further decreased by the action of the pilo-motor muscles, which when in contraction or in a state of greater tonicities render the skin tenser and thus press out the blood and tissue juices. The secretion of sweat is diminished, so that the quantity of heat lost in the vaporization of water is decreased. On the other hand, heat-dissipation tends to be materially increased by the greater radiation of heat due to the greater difference between the temperature of the body and of the douche, bath, etc., and the tendency to an increase in this way is much greater than the opposite tendency depending upon the factors above noted, therefore heat-



dissipation is increased. Bathing the skin with cold water increases heat-loss by the vaporization of water as well as by conduction.

The excitation of the cutaneous nerves by cold reflexly increases thermogenesis, and to such an extent that heat-production may even exceed the quantity dissipated, thus causing an increase of bodily temperature. This rise, which is transient, may amount to  $0.2^{\circ}$  C. or more, and is followed by a reaction in which the temperature may fall  $0.2^{\circ}$  C. or more below the normal, and continue subnormal for some hours; this fall in turn is succeeded by a supplementary reaction in which the temperature may rise slightly above the normal.

The chief reactions brought about by moderate external cold are constriction of the cutaneous blood-vessels, a diminution of the quantity of sweat secreted, increased tonicity of the pilo-motor muscles, and increased tonicity of the skeletal muscles. The action upon the latter muscles may be so marked as to cause shivering, which increases respiratory activity (see p. 432) and presumably similarly increases heat-production.

Moderate external heat causes dilatation of the cutaneous vessels, excites the general circulation and thus increases the blood-supply to the skin, excites respiratory movements and the sweat-glands, but decreases thermogenesis. Owing to the dilatation of the blood-vessels of the skin and the excitation of the circulation the temperature and the quantity of the blood supplied to the skin are increased, so that conditions are caused which are favorable to an increased loss of heat by radiation. Increased activity of the respiratory movements means a larger volume of air respired, and consequently a greater loss of heat in warming the air and in the evaporation of the larger quantity of water from the lungs. The increase in the quantity of sweat formed also favors heat-dissipation by means of the larger amount of water evaporated from the skin. External heat also causes diminished tonicity of the muscles, and consequent diminished thermogenesis which is probably due to a lessening of the activity of the chemical changes in the muscles.

When external temperature is excessive and continued, heat-regulation is rendered impossible: if extreme cold, heat-dissipation takes place more rapidly than heat-production, so that bodily temperature falls until death results; if extreme heat, heat-dissipation is so interfered with that heat accumulates within the organism, causing a continuous rise of temperature which finally causes death.

*Abnormal Thermotaxis.*—By this term is meant the regulation of the heat-processes under conditions in which the mean bodily temperature is maintained at a standard above or below the normal, as in fever and in animals from which the hair has been shaved. It is assumed that under normal conditions the heat-centres are "set," as it were, for a given temperature of the blood, and that when the temperature of the blood goes above or below this standard a compensatory reaction occurs, so that thermogenesis and thermolysis are properly affected to bring about an adjustment. In fever it may be considered that the centres are set for a higher temperature than the normal; the higher the fever, the higher the adjustment. The centres may be set for subnormal

temperatures, as in the case of a rabbit shaved, whose temperature may remain 2° or 3° below the normal for a week or more. When the cause of the abnormal condition disappears, the centres are readjusted to the normal standard.

#### E. POST-MORTEM RISE OF TEMPERATURE.

A rise of temperature after death is not uncommon; indeed, in case of violent death of healthy individuals, and after death following convulsions, a rise in temperature is almost invariable. This increase is due to continued heat-production and to diminished heat-dissipation. Heat-production after death may be due to continued chemical activity in the muscles and other structures which are not dead but simply in a moribund state. There is, as it were, a residual metabolic activity which remains in the cells until their temperature has been reduced to such a standard that the molecular transformations cease—in other words, until the death of the cells occurs. Consequently, the higher the temperature of the individual at the time of somatic death (the cessation of the circulation and respiration), the longer heat-production continues, because the longer the time required to cool the cells to such a degree that their chemical processes no longer go on. Heat is also produced during the development of rigor mortis. The more quickly rigor sets in, and the more intense it is, the greater is the abundance of heat produced.

The tendency to an increase of bodily temperature is favored by the marked diminution of heat-dissipation which occurs immediately upon the cessation of the circulation and respiration. Therefore, while both heat-production and heat-dissipation fall at once and enormously at the time of death, heat-dissipation may be decreased to a more marked degree than heat-production, so that heat may accumulate and the bodily temperature rise.

*Temperature Sense.*—(See Cutaneous Sensibility, in the section on Special Senses.)





## IX. THE CHEMISTRY OF THE ANIMAL BODY.

**Introduction.**—Living matter contains hydrogen, oxygen, sulphur, chlorine, iodine, fluorine, nitrogen, phosphorus, carbon, silicon, potassium, sodium, calcium, magnesium, and iron. Abstraction of one of these elements means death to the organism. The compounds occurring in living matter may for the most part be isolated in the laboratory, but they do not then exhibit the properties of animate matter. In the living cell the smallest particles of matter are arranged in such a manner that the phenomena of life are possible. Such an arrangement of materials is called *protoplasm*, and anything which disturbs this arrangement results in sickness or in death. Somatic death may result from physical shock to the cell; or it may be due to the inability of the cell or the organism to remove from itself poisonous products which are retained in the body so affecting the smallest particles that functional activity is impossible. Pure chemistry adds much to our knowledge of physiology, but it must always be remembered that the conditions present in the beaker glass are not the conditions present in the living cell, for physical and chemical results are dependent on surrounding conditions; hence the necessity and value of animal experimentation. From chemical changes, the physical activities, *i. e.* the motions characteristic of life, result. Hence the chemistry of protoplasm is the corner-stone of biology. The plan of this section is designed to consider the substances concerned in life in the order usually followed by chemical text-books, and to compare as far as possible the results obtained in pure chemistry with the chemical changes in the organism.

### THE NON-METALLIC ELEMENTS.

#### HYDROGEN, $H = 1$ .

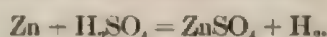
This gas is found as a constant product of the putrefaction of animal matter, and is therefore present in the intestinal tract. It is found in the expired air of the rabbit and other herbivorous animals, and in traces in the expired air of carnivorous animals, having first been absorbed by the blood from the intestinal tract. By far the greater amount of hydrogen in the animal and vegetable worlds, as well as in the world at large, occurs combined in the form of water, and it will be shown that the proteids, carbohydrates, and fats, characteristic of the organism, all contain hydrogen originally derived from water. In the atmosphere is found ammonia in traces, which holds hydrogen in combination, and this is a second source of hydrogen, especially for the construction of the proteid molecule.

**Preparation.**—(1) Through the electrolysis of water, by which one volume

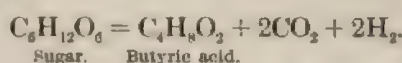


of oxygen is evolved on the positive pole and two volumes of hydrogen on the negative.

(2) Through the action of zinc on sulphuric acid,<sup>1</sup>

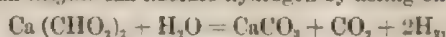


(3) Through putrefaction (by which is understood the change effected in organic matter through certain lower organisms, *bacteria*) hydrogen is liberated in the intestinal canal from proteid matter, and especially from the fermentation of carbohydrates:



In putrefaction in the presence of oxygen the hydrogen formed immediately unites with oxygen, producing water; hence, notwithstanding the enormous amount of putrefaction in the world, there is no accumulation of hydrogen in the atmosphere.

Both bacteria and an *enzyme* can liberate hydrogen by acting on calcium formate,



and this same reaction may be brought about by the action of metallic iridium, rhodium, or ruthenium on formic acid. An *enzyme* is a substance probably of proteid nature capable of producing change in other substances without itself undergoing apparent change (example, pepsin). Bunge<sup>2</sup> calls attention to the fact that the above reaction may be brought about by living cells (bacteria), by an organic substance (enzyme), and by an inorganic metal. This similarity of action between organized and unorganized material, between living and dead substances, is shown more and more conspicuously as science advances.

*Properties.*—Hydrogen burns in the air, forming water, and if two volumes of hydrogen and one of oxygen be ignited, they unite with a loud explosion. Hydrogen will not support respiration, but, mixed with oxygen, may be respired, probably being dissolved in the fluids of the body as an inert gas, without effect upon the organism. Hydrogen may pass through the intestinal tissues into the blood-vessels, according to the laws of diffusion, in exchange for some other gas, and may then be given off in the lungs. *Nascent hydrogen*—that is to say, hydrogen at the moment of generation—is a powerful reducing agent, uniting readily with oxygen (see p. 505).

#### OXYGEN, O — 16.

Oxygen is found free in the atmosphere to the amount of about 21 per cent. by volume, and is found dissolved in water and chemically combined in arterial blood. It is swallowed with the food and may be present in the stomach, but it entirely disappears in the intestinal canal, being absorbed by respiratory exchange through the mucous membrane. It occurs chemically combined with metals so that it forms one-half the weight of the earth's crust; it likewise occurs combined in water and in most of the materials forming animal and vegetable organisms. It is found in the blood in loose chemical

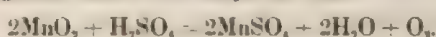
<sup>1</sup> It is not within the scope of this work to give more than typical methods of laboratory preparation. For greater detail the reader is referred to works on general chemistry.

<sup>2</sup> *Physiologische Chemie*, 2d ed., 1889, p. 167.

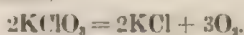
combination as oxyhæmoglobin. It is present dissolved in the saliva, so great is the amount of oxygen furnished by the blood to the salivary gland; it is, however, not found in the urine or in the bile.

*Preparation.*—(1) Through the electrolysis of water (see Hydrogen).

(2) By heating manganese dioxide with sulphuric acid,



(3) By heating potassium chlorate,

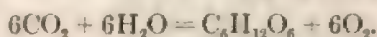


(4) By the action of a vacuum, or an atmosphere containing no oxygen, on a solution of oxyhæmoglobin,



This latter is the method occurring in the higher animals. Any oxygen present in a cell in the body combines with the decomposition products formed there, consequently entailing in such a cell an oxygen *vacuum*, which now acts upon the oxyhæmoglobin of the blood-corpuscles in an adjacent capillary, *dissociating* it into oxygen and hæmoglobin.

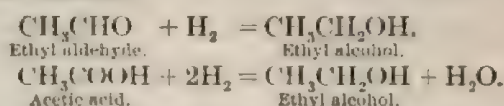
(5) By the action of sunlight on the leaf of the plant, transforming the carbonic oxide and water of the air into sugar, and setting oxygen free,



*Properties.*—All the elements except fluorine unite with oxygen, and the products are known as oxides, the process being called oxidation. It is usually accompanied by the evolution of energy in the form of heat, and often the energy liberated is sufficiently great to cause the production of light. The light of a candle comes from vibrating particles of carbon in the flame, which particles collect as lampblack on a cold plate. In pure oxygen combustion is more violent than in the air; thus, iron burns brilliantly in pure oxygen, while in damp air it is only very slowly converted into oxide (rust). This latter process is called slow combustion, and animal metabolism is in the nature of a slow combustion. In the burning candle has been noted the liberation of heat, and motion of the smallest particles: in the cell there is likewise oxidation, with dependent liberation of heat and motion of the smallest particles in virtue of which the cell is active. Phenomena of life are phenomena of motion, and the energy supplying this motion comes from chemical decomposition. The amount of oxidation in the animal is not increased in an atmosphere of pure oxygen, nor, within wide limits, is it affected by variations in atmospheric pressure, for oxygen is not the *cause* of decomposition. In putrefaction it is known that bacteria cause decomposition, and the products subsequently unite with oxygen. But the cause of the decomposition in the cell remains unsolved, it being only known that the decomposition-products after being formed unite with oxygen. So the quantity of oxygen absorbed by the body depends on the decomposition going on, not the decomposition on the absorption of oxygen. This distinction is fundamental (see further under Ozone and Peroxide of Hydrogen).

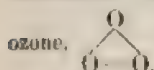


By *reduction* in its simplest sense is meant the removal of oxygen wholly or in part from the molecule. Example: reduced hæmoglobin from oxy-hæmoglobin, iron from oxide of iron ( $\text{Fe}_2\text{O}_3$ ). Reduction may likewise be accomplished by simple addition of hydrogen to the molecule, or by the substitution of hydrogen for oxygen. These two processes may be represented respectively by the reactions:

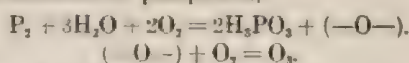


**Ozone,  $\text{O}_3$ .**—Ozone is a second form of oxygen possessing more active oxidizing properties than common oxygen. It is found in neighborhoods where large quantities of water evaporate, and after a thunder-storm.

*Preparation.*—(1) An induction current in an oxygen atmosphere breaks up some of the molecules present into atoms of nascent or "active" oxygen  $-\text{O}-$ , the powerful affinities of whose free bonds enter into combination with oxygen,  $\text{O}=\text{O}$  to form



(2) Through the slow oxidation of phosphorus,



(3) On the positive pole in the electrolysis of water.

In each of the above cases ozone is formed by the action of nascent oxygen on oxygen.

*Properties.*—Ozone is a colorless gas, hardly soluble in water, and having the peculiar smell noted in the air after thunder-storms. Ozone has powerful oxidizing properties due to its third unstable atom of oxygen, oxidizing silver, which oxygen of itself does not. But ozone is not as oxidizing as nascent or "active" oxygen, which may convert carbon monoxide into dioxide, and nitrogen into nitrous acid. Ozone cannot occur in the cell, as any nascent oxygen formed would naturally unite not with oxygen, but with the more readily oxidizable materials of the cell itself. Ozone acts on an alcoholic solution of guaiacum, turning it blue; blood-corpuscles give the same reaction with guaiacum, hence it was thought that hæmoglobin converted oxygen into ozone. However, this test is not a test for ozone, but for "active" atomic oxygen, which is produced from the ozone and in the decomposing blood-corpuscle (see theory of Traube below, and that of Hoppe-Seyler under Peroxide of Hydrogen). Ozone converts oxyhæmoglobin into methæmoglobin.

*Theory of Traube as to the Cause of Oxidation in the Body.*—Indigo-blue dissolved in a sugar-solution gives up oxygen in the atomic state for the oxidation of sugar, and the solution becomes white. If shaken in the air the blue coloration reappears, owing to the absorption of oxygen by the indigo. Hence indigo has the power of splitting oxygen into atoms, and acts as an "oxygen-carrier" between the air and the sugar. Traube is of the opinion that an "oxygen-carrier" exists in the blood-corpuscles. Sugar is destroyed by standing in fresh defibrinated blood; serum alone does not effect this, nor does a solution of oxyhæmoglobin, but it may take place in the extract obtained by

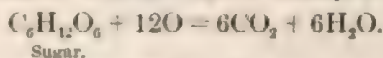
the action of a 0.6 per cent. sodium-chloride solution on blood-corpuscles.<sup>1</sup> The action here has been described as that of *catalysis*, that is, an action by which some substance effects decomposition in another substance without permanent change in itself. In this case the substance in the blood-corpuscle is defined as an "oxygen-carrier," taking molecules of oxygen from oxy-hæmoglobin and giving atomic oxygen for the oxidation of the sugar. Spitzer<sup>2</sup> has shown that these oxygen-carriers are iron-containing nucleoproteids which are characteristic constituents of the cellular nucleus. Hence the nucleus is the principal oxidation organ of living matter. Separation of protoplasm from its nucleus causes the death of the protoplasm on account of decreased oxidative capacity.<sup>3</sup>

Old turpentine is highly oxidizing. This action was once believed to be due to absorbed ozone. If old turpentine be mixed with water and filtered, the aqueous extract has the same properties, due to the fact that an oxidized product which is soluble in water, gives off, under favorable conditions, atomic oxygen.<sup>4</sup>

**Water, H<sub>2</sub>O.**—Water is found on the earth in large quantities, and its vapor is a constant constituent of the atmosphere. It is a product of the combustion of animal matter, and occurs in expired air almost to the point of saturation. It is furthermore given off by the kidneys and by the skin. It is a necessary constituent of a living cell, and forms 67.6 per cent. of the weight of the human body (Moleschott). Removal of 5 to 6 per cent. of water from the body, as for example in cholera, causes the blood to become very viscid and to flow slowly, no urine is excreted, the nerves become excessively irritable, and violent convulsions result.<sup>5</sup>

*Preparation.*—(1) By passing an electric spark through a mixture of one volume of oxygen and two volumes of hydrogen.

(2) By the combustion of a food—as, for example,



(3) *Distilled water* is made in quantity by boiling ordinary water and condensing the vapors formed in another vessel.

*Properties.*—Water is an odorless, tasteless fluid of neutral reaction, colorless in small quantities, but bluish when seen in large masses. It is a bad conductor of heat and electricity. It conducts electricity better when it contains salts. It is nearly non-compressible and non-expansible; thus in plant-life, through evaporation on the surface of the leaf, sap is continuously attracted from the roots of the tree. The solvent properties of water give to the blood many of its uses, soluble foods being carried to the tissues and soluble products of decomposition to the proper organs for elimination.

When water is absorbed by any substance the process is called *hydration*,

<sup>1</sup> Read W. Spitzer: *Pflüger's Archiv*, 1895, Bd. 60, S. 307.      <sup>2</sup> *Ibid.*, 1897, Bd. 67, S. 615.

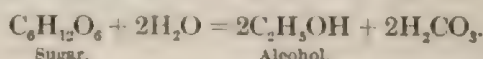
<sup>3</sup> J. Loeb: *Archiv für Entwicklungsmechanik der Organismen*, 1899, Bd. 8, S. 689.

<sup>4</sup> N. Kowalewsky: *Centralblatt für die medicinische Wissenschaft*, 1889, S. 113.

<sup>5</sup> C. Voit: *Hermann's Handbuch*, 1881, Bd. vi 1, S. 349.



as an example of which may be cited the change of calcium oxide into hydroxide when thrown into water. When a substance breaks down into simpler bodies through absorption of water the process is called *hydrolysis* or *hydrolytic cleavage*. Thus cane-sugar may take up water and be resolved into a mixture of dextrose and levulose, which are called *cleavage-products*. So, likewise, starch and proteid are resolved into series of simpler bodies through hydrolytic cleavage—changes which take place in intestinal digestion. All forms of fermentation and putrefaction are characterized by hydrolysis (examples, p. 500), and hence complete drying prevents such processes. Alcoholic, butyric, and lactic fermentation are apparent though not real exceptions to the above. Alcoholic fermentation, for example, is usually represented by the reaction,  $C_6H_{12}O_6 = 2C_2H_5OH + 2CO_2$ , but the  $CO_2$  is in fact united with water, and hence the true reaction should read,



*Drinking-water* contains salts and air dissolved, giving it an agreeable taste. One does not willingly take distilled water on account of its tastelessness.

Dry animal membranes and cells absorb water in quantities varying with the concentration and the quality of salts in the solution in which they are suspended (Liebig). This is called *imbibition*. Membranes will absorb a solution of potassium salts in greater quantity than of sodium salts, and so the potassium salts are found predominating in the cells, the sodium salts in the fluids of the body. A blood-corpuscle treated with distilled water swells because it can hold more distilled water than it can salt-containing plasma. A corpuscle placed in a 0.65 per cent. solution of sodium chloride (the physiological salt-solution) remains unchanged, for this corresponds in concentration to the plasma of the blood. If the corpuscle be placed in a strong solution of a salt it shrivels, because it cannot hold as much of that solution as it can one having the strength of the salts of the plasma. Oysters are often planted at the mouths of fresh-water rivers, since they imbibe more of the weaker solution and appear fatter. If salt be placed on meat and left to itself, a brine is formed around the meat on account of the osmotic pressure exerted by the strong solution of salt, which sets up an osmotic stream of water to the salt and thus deprives the meat of water.

Different bodies require different quantities of heat to warm them to the same extent. The amount of heat required to raise the temperature of water is greater than that for any other substance. A *calorie* or heat-unit is the amount of heat required to raise 1 cubic centimeter of water from 0° to 1° C. The *specific heat* of the human body—that is, the amount of heat required to raise 1 gram 1° C.—is about 0.8 that of water. On the transformation of a substance from the solid to the liquid state, a certain amount of heat is absorbed, known as *latent heat*. To melt 1 gram of ice producing 1 gram of water at 0°, 79 calories are required, or sufficient to raise 1 gram of water from 0° to 79°. Upon the basis of these facts a determination may be made by means of the *ice-calorimeter* of the number of heat-units produced in the combustion. For example, 1 gram of sugar (dextrose) burned in an ice-chamber, melts 49.86 grams of ice. Since each gram required 79 calories to melt it, 3939 calories must have been produced altogether. If 1 gram of sugar be burned in the body, the heat produced is identically the same, and may be measured with great accuracy.<sup>1</sup>

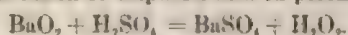
In the transformation of water at 100° to steam at 100° there is a further absorption of

<sup>1</sup> M. Rubner: *Zeitschrift für Biologie*, 1893, Bd. 30, S. 73.

heat, the latent heat of steam. For 1 gram of water this absorption amounts to 536.5 calories. This property of water is of great value to life, for through the heat absorbed in the evaporation of sweat the temperature of the body is in part regulated.

**Peroxide of Hydrogen,  $H_2O_2$ ,** is found in very small quantities in the air, in rain, snow, and sleet, and where there is oxidation of organic matter.

*Preparation.*—(1) By the action of sulphuric acid on peroxide of barium,



(2) Peroxide of hydrogen is a product of the oxidation of phosphorus, and generally exists wherever ozone is produced.

(3) Peroxide of hydrogen exists wherever nascent hydrogen acts on oxygen. It is therefore found mixed with hydrogen evolved at the negative pole in the electrolysis of water. This action happens in putrefaction, where the nascent hydrogen unites with any oxygen present, and the resulting  $H_2O_2$  strongly oxidizes the organic matter through the free  $-O-$  atom liberated.<sup>1</sup>

*Properties.*—Peroxide of hydrogen is a colorless, odorless, bitter-tasting fluid, which decomposes slowly at 20° F., and with great violence at higher temperatures. It oxidizes where ordinary oxygen is ineffective; it is a powerful bleaching agent, and is used to produce blonde hair. It destroys bacteria. Blood-corpuscles brought into a solution of  $H_2O_2$  bring about its rapid decomposition into water and atomic oxygen, whereby oxygen is evolved and oxyhæmoglobin is converted into methæmoglobin. If oxyhæmoglobin be brought into a putrefying fluid, the nascent hydrogen withdraws oxygen from combination to form  $H_2O_2$ , and then the atomic oxygen reacts on hæmoglobin to form methæmoglobin.<sup>2</sup> The formula for the peroxide is probably  $H-O-O-H$ . In certain cases peroxide of hydrogen has a reducing action.

*Theory of Hoppe-Seyler<sup>3</sup> to account for the Oxidation in the Body.*—This maintains that, as in putrefaction, hydrogen is produced in the decomposition of the cell, and acting on the oxygen present converts it into peroxide with its unstable atom, which then splits off as active oxygen and effects the oxidation of the substances in the cell. This theory is easier to reconcile with the fact that oxidation is dependent on the amount of decomposition (see p. 501) than is the theory of Traube.

Solutions of  $H_2O_2$  do not liberate iodine from potassium iodide immediately, but only on the addition of blood-corpuscles or of ferrous sulphate, which cause liberation of  $-O-$ , and then any starch present may be colored blue (see p. 502). Guaiacum is not affected by  $H_2O_2$ , unless blood-corpuscles or ferrous sulphate be added to make the oxygen active.

#### SULPHUR, S = 32.

Sulphur is built in the proteid molecule of the plant from the sulphates taken from the ground. It is found in albuminoids, especially in keratin. As taurin it occurs in muscle and in bile, as iron and alkaline sulphide in the

<sup>1</sup> Hoppe-Seyler: *Zeitschrift für physiologische Chemie*, 1878, Bd. 2, S. 22.

<sup>2</sup> Hoppe-Seyler, *Op. cit.*, S. 26.

<sup>3</sup> *Pflüger's Archiv*, Bd. 12, S. 16, 1876. See also *Berichte der deutschen chemischen Gesellschaft*, Bd. 22, S. 2215.



feces, as sulphuretted hydrogen in the intestinal gas, as sulphate and other unknown compounds in the urine.

**Sulphuretted Hydrogen,  $H_2S$ .**—This gas is found in the intestines, and pathologically in the urine.

*Preparation.*—(1) Action of hydrochloric or sulphuric acid on ferrous sulphide,



This same reaction takes place by treating feces (which contain  $FeS$ ) with acid.

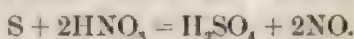
(2) From the putrefaction of proteids, and by boiling proteid with mineral acid.

*Properties.*—Sulphuretted hydrogen unites readily with the alkalies and with iron salts, forming sulphide; hence little  $H_2S$  is found in the intestinal tract. It is a strong poison when respired. It has been shown to enter into combination with oxyhæmoglobin to form sulph-hæmoglobin, and likewise in frogs it rapidly kills the nerves.<sup>1</sup> Sulphuretted hydrogen diluted with hydrogen and introduced into the rectum of a dog produces symptoms of poisoning in one to two minutes (Planer). It has an offensive odor similar to foul eggs.

**Sulphurous Acid,  $H_2SO_3$ .**—This acid has been found in the urine of cats and dogs, and has been detected by Strümpell in human urine in a case of typhoid fever.

**Sulphuric Acid,  $H_2SO_4$ .**—This acid is found in the urine in combination with alkali (preformed sulphate), and with indol, skatol, cresol, and phenol (etheral sulphates). It is found in the saliva of various gastropods.

*Preparation.*—(1) By oxidation of sulphur with nitric acid,



(2) By oxidation of sulphur-containing proteid.

*Properties.*—Sulphuric acid is a very powerful acid. It is produced in the body by the burning of the proteids (which contain 0.5 to 1.5 per cent. S), 80 per cent. or more being oxidized to acid, while the remainder appears in the urine in the unoxidized condition termed *neutral sulphur*. When proteid, fat, and starch free from ash are fed to dogs, they live only half as long as they would were they starving,<sup>2</sup> for, according to Bunge,<sup>3</sup> the sulphuric acid formed abstracts necessary salts from the tissue. (For further discussion of this see pp. 554 and 525).

If 100 cubic centimeters of urine be treated with 5 cubic centimeters of hydrochloric acid and barium chloride be added, the *preformed* sulphuric acid is precipitated as barium sulphate ( $BaSO_4$ ), which may be washed, dried, and weighed. If 100 cubic centimeters of urine be mixed with an equal volume of a solution containing barium chloride and hydrate, filtered, and one-half the filtrate (= 50 cubic centimeters of urine, now free of *preformed* sulphate) be strongly acidified with hydrochloric acid and boiled, the etheral sulphates will be broken up, and the resulting precipitate of barium sulphate will correspond to the *etheral* sulphuric acid. To determine the *neutral* sulphur, evaporate the

<sup>1</sup> Harnack: *Archiv für experimentelle Pathologie und Pharmacologie*, 1894, Bd. 34, S. 156.

<sup>2</sup> J. Foster: *Zeitschrift für Biologie*, 1873, Bd. 9, S. 297.

<sup>3</sup> *Physiologische Chemie*, 2d ed., 1889, p. 104.

urine to dryness, fuse the residue with potassium nitrate ( $\text{KNO}_3$ ), which oxidizes all the sulphur to sulphate, take up with water and hydrochloric acid, add barium chloride, and the precipitate ( $\text{BaSO}_4$ ) represents the total sulphur present. Deduct the amount belonging to sulphuric acid, previously determined, and the remainder represents the neutral sulphur.

**METABOLISM OF SULPHUR.**—The total amount of sulphur in the urine runs proportionally parallel with the amount of nitrogen; that is to say, the amount is proportional to the amount of proteid destroyed. The amount of ethereal sulphate is dependent upon the putrefactive production of indol, skatol, phenol, and cresol in the intestinal canal, which on absorption form a synthetical combination with the traces of sulphate in the blood. Concerning neutral sulphur it is known that taurin is one source of it. If taurin be fed directly, the amount of neutral sulphur in the urine increases (Salkowski), and in a dog with a biliary fistula the neutral sulphur decreases but does not entirely disappear.<sup>1</sup> In a well-fed dog with a biliary fistula Voit<sup>2</sup> found the quantity of sulphur in the bile to be about 10 to 13 per cent. of that in the urine. This biliary sulphur (taurin) is normally reabsorbed, as the quantity of sulphur in the feces ( $\text{FeS}$ ,  $\text{Na}_2\text{S}$ ) is small and derived principally from proteid putrefaction. The amount of neutral sulphur in the urine is greatest under a meat diet, least when fat or gelatin is fed; the sulphur of gelatin is very small in quantity. In dyspnoea the amount of neutral sulphur increases in the urine, on account of insufficient oxidation.<sup>3</sup> The neutral sulphur of the urine includes potassium sulphocyanide (originally derived from the saliva), likewise a substance which on treatment with calcium hydrate yields ethyl sulphide,  $(\text{C}_2\text{H}_5)_2\text{S}$ ,<sup>4</sup> and there are present other unknown compounds (see p. 547). When an animal eats proteid and neither gains nor loses the same in his body, the amount of sulphur ingested is equal to the sum of that found in the urine and feces. If sulphur be eaten, it partially appears as sulphate in the urine. Sulphates eaten pass out through the urine. They play no part in the life of the cell.

CHLORINE,  $\text{Cl} = 35.5$ .

Free chlorine is not found in the organism, and when breathed it vigorously attacks the respiratory mucous membranes. Chlorine is found combined in the body as sodium, potassium, and calcium chlorides, as hydrochloric acid, and it is said to belong to the constitution of pepsin.<sup>5</sup>

**Hydrochloric Acid,  $\text{HCl}$ ,** is found to a small extent in the gastric juice.

**Preparation.**—(1) If sunlight acts on a mixture of equal volumes of chlorine and hydrogen, they unite with a loud explosion.

<sup>1</sup> Kunkel: *Archiv für die gesammte Physiologie*, 1877, Bd. 14, S. 353.

<sup>2</sup> *Zeitschrift für Biologie*, 1894, Bd. 30, S. 554.

<sup>3</sup> Harnack and Kleine: *Zeitschrift für Biologie*, 1899, Bd. 37, S. 417.

<sup>4</sup> J. J. Abel: *Zeitschrift für physiologische Chemie*, 1894, Bd. 20, S. 253.

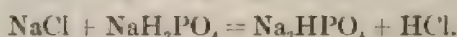
<sup>5</sup> E. O. Schoumow-Simanowski: *Archiv für exper. Pathologie und Pharmakologie*, 1894, Bd. 33, S. 336.



(2) By the action of strong sulphuric acid on common salt,



(3) By the action of primary acid phosphate of sodium on common salt,



This, according to Maly, represents the process in the cells of the gastric glands.

*Properties.*—Hydrochloric acid readily unites with most metals, forming chlorides. It causes a gelatinization of the proteids and seems to unite with them chemically. Such gelatinization is a necessary forerunner of peptic digestion. The cleavage products of peptic digestion (peptones, proteoses, etc.) combine with more hydrochloric acid than the original more complex proteid.<sup>1</sup> Free hydrochloric acid of the strength of the gastric juice (0.2 per cent.) inverts cane-sugar at the temperature of the body,<sup>2</sup> and inhibits the action of bacteria. Hydrochloric acid is derived from decomposition of chlorides in the secreting cells of the stomach. It has been shown that the excretion of common salt in the urine is decreased during those hours that the stomach is active, while the acidity of the urine decreases. If, in a dog with a gastric fistula, the mucous membrane of the stomach be stimulated and the gastric juice be removed as soon as formed, the urine becomes strongly alkaline with sodium carbonate (the excess of Na liberated taking this form) while the chlorides may entirely disappear from the urine.<sup>3</sup> Respiration in an atmosphere containing 0.5 per cent. HCl gas becomes very uncomfortable after twelve minutes.<sup>4</sup>

If the bases (K, Na, Ca, Mg, Fe) of gastric juice and then the acid radicals (Cl and  $\text{P}_2\text{O}_5$ ) be determined, and the phosphoric anhydride be united with the proper bases, and then chlorine with the rest of the bases, there still remains an excess of chlorine which can only have belonged to the hydrochloric acid present. To detect free hydrochloric acid put three or four drops of a saturated alcoholic solution of tropæolin 00 in a small white porcelain cover, add to this an equal quantity of gastric juice, evaporate slowly, and the presence of hydrochloric acid is shown by a beautiful violet color, not given by any organic acid.<sup>5</sup> Günzburg's reagent consisting of phloroglucin and vanillin in alcoholic solution, warmed (as above) with gastric juice containing free hydrochloric acid, gives a carmine-red mirror on the porcelain, not given by an organic acid.<sup>6</sup>

CHLORINE IN THE BODY is ingested as chloride, and leaves the body as such, principally in the urine, likewise through the sweat and tears, and in traces in the feces.

#### BROMINE, Br = 80.

Salts of bromine are found in marine plants and animals, but their physiological importance has not been established. Bromine is a fluid of intensely disagreeable odor.

<sup>1</sup> Chittenden: *Curtwright Lectures on Digestive Proteolysis*, 1895, p. 52.

<sup>2</sup> Ferris and Lusk: *American Journal of Physiology*, 1898, vol. i. p. 277.

<sup>3</sup> E. O. Schoumow-Simanowski: *Archiv für exper. Pathologie und Pharmakologie*, 1894, Bd. 33, S. 336.

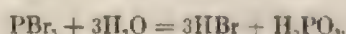
<sup>4</sup> Lehmann: *Archiv für Hygiene*, Bd. 5, S. 1.

<sup>5</sup> Boas: *Deutsche medicinische Wochenschrift*, 1887, No. 39.

<sup>6</sup> Günzburg: *Centralblatt für klinische Medizin*, 1887, No. 40.

whose vapors strongly attack the skin, turning it brown, and likewise the mucous membranes of the respiratory passages.

**Hydrobromic Acid**,  $\text{HBr}$ , may be prepared by the action of water on phosphorus tribromide,



It is a colorless gas of penetrating odor. If sodium bromide be given to a dog in the place of sodium chloride, fifty per cent. and more of the hydrochloric acid may be supplanted by hydrobromic acid in the gastric juice.<sup>1</sup> The various organs are then found to contain bromine, especially the kidneys<sup>2</sup> through which it may be eliminated.

#### IODINE, $\text{I} = 127$ .

Like bromine, the salts of iodine are found in many marine plants and animals, especially in the *algæ*. It is found in the thyroid gland. Iodine is prepared in metallic-looking plates, almost insoluble in water, but soluble in alcohol (tincture of iodine). Iodine is still more strongly corrosive in its action on animal tissue than is chlorine or bromine, and is an antiseptic and disinfectant. A slight trace of free iodine turns starch blue.

**Hydriodic Acid**,  $\text{HI}$ , is prepared like hydrobromic acid, by the action of water on tri-iodide of phosphorus. An aqueous solution of hydriodic acid introduced into the stomach is absorbed, and shortly afterward iodine, as alkaline iodide, may be detected in the urine. On administration of sodium iodide to a dog with his food, only very little hydriodic acid appears in the gastric juice.<sup>3</sup>

**CIRCULATION IN THE BODY.**—Iodine or iodides given are rapidly eliminated in the urine, in smaller amounts in saliva, gastric juice, sweat, milk, etc. It is noticed that for weeks after the administration of the last dose of potassium iodide, traces of iodine are found in the saliva, and none in the urine. The explanation lies in the presumption that iodine has been united with proteid to a certain extent, and appears in such secretions as saliva, which contains materials derived from proteid through glandular manufacture.<sup>4</sup> A similar explanation avails in the case of Drechsel's<sup>5</sup> discovery that, in patients who have been treated with iodides, iodine may be detected in the hair (the keratin of hair being derived from other proteid bodies.) Whether free iodine or hydriodic acid is liberated in the tissues from ingested iodides are disputed points. Baumann<sup>6</sup> discovered an organic compound of iodine occurring in the thyroid gland and containing as much as 9.3 per cent. of iodine. Ross<sup>7</sup> states that this thyroiodine from sheep's thyroid constantly contains about 5 per cent. of iodine. When fed it increases the metabolism of proteid and fat<sup>8</sup> and acts as an antitoxine. According to Blum,<sup>9</sup> the iodine is combined with the proteids of the thyroid in varying quantity, and any liberated iodine may act within the thyroid to destroy toxic bodies, especially nerve toxins.<sup>10</sup> Oswald,<sup>11</sup> on the contrary, states that the effective principle of the thyroid is a thyroglobulin containing 1.66 per cent. of iodine. This thyroglobulin treated with acids yields thyroiodine, which contains 14.4 per cent. of iodine. Thyroids which contain no iodine have no physiological effect upon metabolism.<sup>12</sup>

<sup>1</sup> Nencki and Schoumow-Simanowski: *Archiv für exper. Pathologie und Pharmacologie*, 1895, Bd. 34, S. 320.

<sup>2</sup> Rosenthal: *Zeitschrift für physiologische Chemie*, 1896, Bd. 22, S. 227.

<sup>3</sup> Nencki and Schoumow-Simanowski: *Loc. cit.*

<sup>4</sup> Schmiedeberg: *Grundriss der Arzneimittellehre*, 24 ed., 1888, S. 197.

<sup>5</sup> *Centralblatt für Physiologie*, 1896, Bd. 9, S. 704.

<sup>6</sup> *Zeitschrift für physiologische Chemie*, 1895, Bd. 21, S. 319. <sup>7</sup> *Ibid.*, 1898, Bd. 25, S. 1.

<sup>8</sup> Voit, F.: *Zeitschrift für Biologie*, 1897, Bd. 35, S. 116.

<sup>9</sup> *Zeitschrift für physiologische Chemie*, 1898, Bd. 26, S. 160.

<sup>10</sup> Blum: *Philips's Archiv*, 1899, Bd. 77, S. 70.

<sup>11</sup> *Zeitschrift für physiologische Chemie*, 1899, Bd. 27, S. 14.

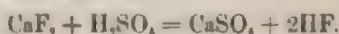
<sup>12</sup> Ross, E.: *Ibid.*, 1899, Bd. 28, S. 40.



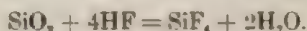
## FLUORINE, F = 19.

Fluorine is found in the bones and teeth, in muscle, brain, blood, and in all investigated tissues of the body, though in minute quantities. In one liter of milk 0.0003 gram of fluorine have been detected.<sup>1</sup> Fluorine is found in plants, and in soil without fluorine plants do not flourish. It seems to be a necessary constituent of protoplasm. Free fluorine is a gas which cannot be preserved, as it unites with any vessel in which it is prepared.

**Hydrofluoric Acid**, HF, is prepared by heating a fluoride with concentrated sulphuric acid, in a platinum or lead dish,



*Properties.*—Hydrofluoric acid is a colorless gas, so powerfully corrosive that breathing its fumes results fatally. Its aqueous solutions are stable, but can be kept only in vessels of platinum, gold, lead, or india-rubber. It etches glass, uniting to form volatile silicon fluoride,



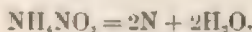
**CIRCULATION IN THE BODY.**—Tappeiner and Brandl<sup>2</sup> have shown, on feeding sodium fluoride (NaF) to a dog in doses varying between 0.1 and 1 gram daily, that the fluorine fed was not all recoverable in the urine and feces, but was partially stored in the body. On subsequently killing the dog, fluorine was found in all the organs investigated, and was especially found in the dry skeletal ash to the extent of 5.19 per cent, reckoned as sodium fluoride. From the microscopic appearance of the crystals seen deposited in the bone, the presence of calcium fluoride was concluded. In this form it normally occurs in bones and teeth.

## NITROGEN, N = 14.

Free nitrogen constitutes 79 per cent. of the volume of atmospheric air. It is found dissolved in the fluids and tissues of the body to about the same extent as distilled water would dissolve it. It is swallowed with the food, may partially diffuse through the mucous membrane of the intestinal tract, but forms a considerable constituent of any final intestinal gas. It is found in the atmosphere combined as ammonium nitrate and nitrite, which are useful in furnishing the roots of the plant with material from which to build up proteid. Bacteria upon the roots of certain vegetables combine and assimilate the free nitrogen of the air (Hellriegel and Willforth). Cultures of *algæ* do the same.<sup>3</sup>

*Preparation.*—(1) By abstraction of oxygen from air through burning phosphorus in a bell jar over water, pentoxide of phosphorus being formed, which dissolves in the water and almost pure nitrogen remains.

(2) By heating nitrite of ammonium,



*Properties.*—Nitrogen is especially distinguished by the absence of chemical affinity for other elements. It does not support combustion, and in it both a

<sup>1</sup> G. Tammann: *Zeitschrift für physiologische Chemie*, 1888, Bd. 12, S. 322.

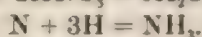
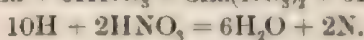
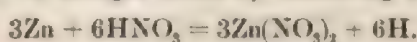
<sup>2</sup> *Zeitschrift für Biologie*, 1892, Bd. 28, S. 518.

<sup>3</sup> P. Kossowitch: *Botanische Zeitung*, 1894, Jahrg. 50, S. 97.

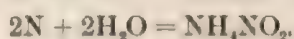
flame and animal life are extinguished, owing to lack of oxygen. It acts as a diluent of atmospheric oxygen, thereby retarding combustion, but on higher animal life it is certainly without direct influence.

**Ammonia**,  $\text{NH}_3$ , is found in the atmosphere as nitrate and nitrite to the extent of one part in one million. It is found in the urine in small quantities, is a constant product of the putrefaction of animal matter, and is a product of trypsin proteolysis.

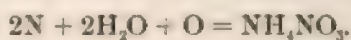
*Preparation.*—(1) Through the action of nascent hydrogen on nascent nitrogen. This may be brought about by dissolving zinc in nitric acid,



Ammonia is produced in a similar way in the dry distillation of nitrogenous organic substances in absence of oxygen, being therefore a by-product in the manufacture of coal-gas. In putrefaction nascent hydrogen acts on nascent nitrogen, producing ammonia, which in the presence of oxygen becomes oxidized to nitrate and nitrite, or in the presence of carbonic oxide is converted into ammonium carbonate. Ammonium nitrite is likewise formed on burning a nitrogenous body in the air, in the evaporation of water, and on the discharge of electricity in moist air,



At the same time a small amount of nitrate is formed in the above three processes,



Hence these substances find their way into every water and soil, and furnish nitrogen to the plant. The value of decaying organic matter as a fertilizer is likewise obvious.

*Properties.*—Ammonia is a colorless gas of pungent odor. It readily dissolves in water and in acids, entering into chemical combination, the radical  $\text{NH}_2$  appearing to act like a metal with properties like the alkalis, and its salts will be described with them. Very small amounts of ammonia instantly kill a nerve, but upon muscular substance it acts first as a stimulant, provoking contractions: 1 part of ammonia in 500 of water will kill an amœba, and 1 part in 10,000 will slow and finally arrest ciliary motion.<sup>1</sup>

**AMMONIA IN THE BODY.**—If it be agreed with Hoppe-Seyler that normal decomposition in the tissues is analogous to putrefaction, then nascent hydrogen acting on nascent nitrogen in the cell produces ammonia, which in the presence of carbonic acid becomes ammonium carbonate, and in turn may be converted into urea by the liver. If acids ( $\text{HCl}$ ) be fed to carnivora (dogs) the amount of ammonia present in the urine is increased, which indicates that an amount of ammonia usually converted into urea has been taken for the neutralization

<sup>1</sup> Bokorny: *Pflüger's Archiv*, 1895, Bd. 59, S. 557.

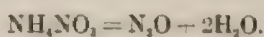


of the acid.<sup>1</sup> In a similar manner acids formed from decomposing proteid may be neutralized (see pp. 506 and 550).

The *ammoniacal fermentation* of the urine consists in the decomposition of urea into ammonium carbonate by the *micrococcus urinae*, the urine becoming alkaline.

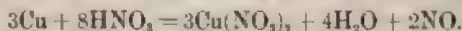
**Compounds of Nitrogen with Oxygen.**—There are various oxides of nitrogen, the higher ones being powerfully corrosive, and some of these unite with water to form acids, of which nitric acid ( $\text{HNO}_3$ ) is the strongest. Only nitrous and nitric oxides are of physiological interest.

**Nitrous Oxide**,  $\text{N}_2\text{O}$ , likewise called "laughing-gas," is prepared by heating ammonium nitrate,



It supports ordinary combustion almost as well as pure oxygen, but it will not sustain life. Mixed with oxygen it may be respired, producing a state of unconsciousness preceded by hysterical laughter.

**Nitric Oxide**,  $\text{NO}$ , is prepared by dissolving copper in nitric acid,



Contact with oxygen converts it into peroxide of nitrogen ( $\text{NO}_2$ ), which is an irritating irrespirable gas of reddish color. Nitric oxide in blood first unites with the oxygen of oxyhæmoglobin, forming the peroxide ( $\text{NO}_2$ ), and then the nitric oxide combines with hæmoglobin, forming a highly stable compound, nitric-oxide hæmoglobin ( $\text{Hb-NO}$ ).

**NITROGEN IN THE BODY.**—Nitrogen is taken into the body combined in the great group of proteid substances, which are normally completely absorbed by the intestinal tract. It passes from the body in the form of simple decomposition-products, in larger part through the urine, but likewise through the juices which pour into the intestinal canal. The unabsorbed residues of these latter juices, mixed with intestinal epithelia constitute in greater part the *feces*.<sup>2</sup> An almost insignificant amount of nitrogen is further lost to the body through the hair, nails, and epidermis, but, generally speaking, the sum of the nitrogen in the urine and feces corresponds to the proteid decomposition for the same time (1 gram  $\text{N} = 6.25$  grams proteid). When the nitrogen of the proteid eaten is equal in quantity to the sum of that in the urine and feces, the body is said to be in *nitrogenous equilibrium*. When the ingested nitrogen has been larger than that given off, proteid has been added to the substance of the body; when smaller, proteid has been lost. These propositions were established by Carl Voit.

A small amount of urea and other nitrogenous substances may be excreted in profuse sweating. Proteid nitrogen never leaves the body in the form of free nitrogen or of ammonia. That ammonia is not given off by the lungs may be demonstrated by performing tracheotomy on a rabbit, and passing the expired air first through pure potassium hydrate (to absorb  $\text{CO}_2$ ) and then through Nessler's reagent. The experiment may be continued for hours with negative result.<sup>3</sup>

<sup>1</sup> Fr. Walther: *Archiv für exper. Pathologie und Pharmacologie*, 1877, Bd. 7, S. 164.

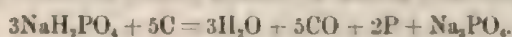
<sup>2</sup> Menichanti and Prausnitz: *Zeitschrift für Biologie*, 1894, Bd. 30, S. 353.

<sup>3</sup> Bachl: *Zeitschrift für Biologie*, 1869, Bd. 5, S. 61.

## PHOSPHORUS, P = 32.

Phosphorus is found combined as phosphate in the soil; it is necessary to the development of plants. As phosphate it is present in large quantity in the bones, and is found also in all the cells, tissues, and fluids of the body, probably in loose chemical combination with the proteid molecule. It is present in nuclein, protagon, and lecithin.

*Preparation.*—Phosphorus was first prepared by igniting evaporated urine,



In a similar way it may be obtained by chemical treatment of bones. The vapors of phosphorus may be condensed by passing them under water, where at a temperature of  $44.4^\circ$  the phosphorus melts and may be cast into sticks.

*Properties.*—Phosphorus is a yellow, crystalline substance, soluble in oils and carbon disulphide. It is insoluble in water, in which it is kept, since in moist air it gives off a feeble glowing light, accompanied by white fumes of phosphorous acid ( $\text{H}_3\text{PO}_3$ ) and small amounts of ammonium nitrate, peroxide of hydrogen, and ozone, to which latter the peculiar odor is ascribed. Phosphorus ignites spontaneously at a temperature of  $60^\circ$ , and this may be produced by mere handling, the resulting burns being severe and dangerous. This form of phosphorus is poisonous, but if it be heated to  $250^\circ$  in a neutral gas (nitrogen) it is changed into red phosphorus, which has different properties and is not poisonous.

*Phosphorus-poisoning.*—On injecting phosphorus dissolved in oil into the jugular vein, embolisms are produced by the oil in the capillaries of the lungs, the expired air contains fumes of phosphorous acid, and the lungs glow when cut out (Magendie). If the phosphorus oil be injected in the form of a fine emulsion, embolism is avoided,<sup>1</sup> and the fine particles of phosphorus are generally distributed throughout the circulation. On autopsy of a rabbit after such injection in the femoral vein, all the organs and blood-vessels glow on exposure to the air.<sup>2</sup> If two portions of arterial blood be taken, and one of them be mixed with phosphorus oil, and they be let stand, both portions become venous in the same time.<sup>3</sup> Hence phosphorus in blood, as in water, is not readily oxidized. Persons breathing vapor of phosphorus acquire phosphorus-poisoning. What the direct action of phosphorus is, is unknown, but the results are most interesting. To understand the results it may be supposed that proteid in decomposing in the body splits up into a *nitrogenous* portion, the nitrogen of which finds its exit through the urine and feces, and a *non-nitrogenous* portion, which is resolved into carbonic oxide and water, just as are the sugars and the fats. This carbonic acid is given off, for the most part, through the lungs. Now if a starving dog, which lives on his own flesh and fat, be poisoned with phosphorus, the proteid decomposition as indicated by the nitrogen in the urine is largely increased, while the amounts of carbonic acid given off and oxygen absorbed are largely decreased; on post-mortem examination the organs are found to contain excessive quantities of fat. We have here presumptive evidence that a part of the proteid molecule usually completely oxidized has not been burned,

<sup>1</sup> L. Hermann: *Pflüger's Archiv*, 1870, Bd. 3, S. 1.

<sup>2</sup> H. Meyer: *Archiv für exper. Pathologie und Pharmacologie*, 1881, Bd. 14, S. 327.

<sup>3</sup> Meyer, *Op. cit.*, S. 329.



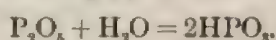
but has been converted into fat.<sup>1</sup> Similar results are characteristic of arsenic and antimony poisoning, and of yellow atrophy of the liver. Rosenfeld has recently shown that much of the fat found in the liver of a dog poisoned with phosphorus is fat transported from the fat repositories of the body (fatty infiltration). The high proteid metabolism, however, of itself would indicate the retention of an unburned part of the proteid molecule, which in this case probably appears as fat<sup>2</sup> (fatty degeneration, see p. 559). A parallel case of high proteid metabolism is seen in diabetes, where sugar from proteid remains unburned.

**Compounds of Phosphorus with Oxygen.**—Of these compounds three oxides and several acids exist, but only meta- and orthophosphoric acid need attention here.

**Phosphorus Peroxide,  $P_2O_5$ ,** is a white powder, which rapidly absorbs moisture; it is produced by burning phosphorus in dry air.

**Metaphosphoric Acid,  $HPO_3$ ,** is said to occur combined in nuclein.

*Preparation.*—(1) By dissolving  $P_2O_5$  in cold water,



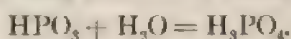
(2) By fusing phosphoric acid,



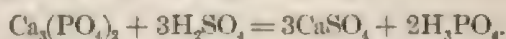
It is converted slowly in the cold, rapidly on heating, into phosphoric acid. Crystalline it forms ordinary glacial phosphoric acid. Metaphosphoric acid precipitates proteid from solution, yielding a body said to be pseudonuclein,<sup>3</sup> but this seems to be untrue<sup>4</sup> (see p. 579).

**Orthophosphoric Acid,  $H_3PO_4$ .**—Salts of this acid constitute all the inorganic compounds of phosphorus in the body, and are called phosphates.

*Preparation.*—(1) By heating solutions of metaphosphoric acid,



(2) By treating bone-ash with sulphuric acid,



*Properties.*—On evaporation of the liquors obtained above, the acid separates in colorless hygroscopic crystals.

Phosphoric acid forms different salts according as one, two, or three atoms of hydrogen are supplanted by a metal. Thus there exist primary sodium or calcium phosphates,  $NaH_2PO_4$  and  $CaH_2PO_4$ ; the secondary phosphates,  $Na_2HPO_4$  and  $CaHPO_4$ ; and the tertiary phosphates,  $Na_3PO_4$  and  $Ca_3(PO_4)_2$ . On account of their reaction to litmus these salts have been falsely called acid, neutral, and basic, but the secondary salts are, chemically speaking, acid salts.

The bones contain a large quantity of tertiary phosphate of calcium; the fluids and cells of the body contain likewise the primary and secondary phos-

<sup>1</sup> J. Bauer: *Zeitschrift für Biologie*, 1871, Bd. 7, S. 63.

<sup>2</sup> Ray, McDermott, and Lusk: *American Journal of Physiology*, 1899, vol. iii. p. 139.

<sup>3</sup> L. Liebermann: *Berichte der deutschen chemischen Gesellschaft*, Bd. 22, S. 598.

<sup>4</sup> Salkowski: *Pflüger's Archiv*, 1894, Bd. 59, S. 245; also, Giertz: *Zeitschrift für physiologische Chemie*, 1899, Bd. 28, S. 115.

phates, while to primary sodium phosphate carnivorous urine mainly owes its acid reaction.

In speaking of the ash of protoplasm, Nencki<sup>1</sup> advocates the idea of separate combinations of the base and acid radicles with the proteid molecule, as, for example, the separate union of potassium with proteid and of phosphoric acid with proteid, in the functionally active cell. However combined, phosphoric acid is necessary for the organism.

**PHOSPHORUS IN THE BODY.**—The principal source of supply is derived from the phosphates of the alkalies and alkaline earths in the foods; it may be absorbed in organic combinations in nuclein, casein, and caseoses; and it may perhaps be absorbed as glycerin phosphoric acid, which is an intestinal decomposition product of lecithin<sup>2</sup> and probably also of protagon. Phosphorus leaves the body almost entirely in the form of inorganic phosphate, the only exception being glycerin phosphoric acid, which has been detected in traces in the urine. In man and carnivora the soluble primary and secondary phosphates of the alkalies are found in the urine, together with much smaller amounts of the less soluble primary and secondary phosphates of the alkaline earths. There is likewise, even during hunger, a continuous excretion of tertiary phosphate of calcium, magnesium, and iron in the intestinal tract. In herbivora the excretion is normally into the intestinal tract, and no phosphates occur in the urine. This is because herbivora eat large quantities of calcium salts which bind the phosphate in the blood, and they likewise eat organic salts of the alkalies, which become converted into carbonate and appear in the urine as acid carbonates; such a urine has no solvent action on calcium phosphate.<sup>3</sup> In a similar manner a great reduction of phosphate in the urine of man may be effected by feeding alkaline citrate and calcium carbonate, the first to furnish the more alkaline reaction to blood and urine, the second to bind the phosphate in the blood. The more alkaline reaction itself is insufficient to prevent the appearance of phosphates in the urine.<sup>4</sup> On the other hand, starving herbivora, or herbivora fed with animal food, give urines acid from primary phosphate.<sup>5</sup> In diabetes where there is a large production of abnormal acids which tend to neutralize the blood, there is a more acid urine which contains an increased amount of calcium phosphate, and the excretion of the same through the intestinal wall correspondingly decreases.<sup>6</sup> During lactation the amount of phosphate eliminated through the ordinary channels is decreased, for a considerable amount is used to form the milk.<sup>7</sup>

Excreted phosphates may be originally derived from the phosphates of the bones, or from phosphates arising from the oxidation of nuclein, protagon, and lecithin, but by far the greater quantity is derived from the food, or from pro-

<sup>1</sup> *Archiv für exper. Pathologie und Pharmacologie*, 1894, Bd. 34, S. 334.

<sup>2</sup> Bökey: *Zeitschrift für physiologische Chemie*, 1877-78, Bd. 1, S. 157.

<sup>3</sup> J. Bertram: *Zeitschrift für Biologie*, 1878, Bd. 14, S. 354.

<sup>4</sup> *Op. cit.*, S. 354.

<sup>5</sup> Weiske: *Ibid.*, 1872, Bd. 8, S. 246.

<sup>6</sup> Gerhardt und Schlesinger: *Archiv für exper. Pathologie und Pharmacologie*, 1899, Bd. 42, S. 83.

<sup>7</sup> Paton, Donlop, and Aitchison: *Journal of Physiology*, vol. xxv. p. 212.



teid metabolism. In a starving dog, which feeds on its own proteid, it was found that a ratio existed between nitrogen and phosphoric acid in the urine as 6.4:1, which approximates that in muscle, *i. e.* 7.6:1. On feeding meat till nitrogenous equilibrium was established, the ratio became 8.1:1.<sup>1</sup> On addition of proteid to the body, a proportionate amount of phosphoric acid is retained for the new protoplasm, while on destruction of proteid the phosphoric acid corresponding to it is eliminated. In diabetes where the proteid metabolism is far above the normal, the phosphorus excretion remains proportional to the proteid destroyed.<sup>2</sup> The larger excretion of phosphoric acid during hunger shown in the ratio above, has been ascribed to the decomposition of the bones.<sup>3</sup> Thus Munk found on Cetti, who lived many days without food, a ratio as low as 4.5:1. In starvation the brain and nerves do not decrease in weight, so the protagon can hardly yield any great amount of phosphoric acid (Voit). Casein and other nucleo-albumins, when fed, are oxidized and furnish phosphoric acid for the urine.

#### CARBON, C = 12.

This element is found combined in every organism, and in many decomposition-products of organized matter. Elementary carbon occurs as lampblack, diamond, and graphite, the two latter having their origin from the action of high heat on coal. Carbon occurs combined in coal, petroleum, and natural gas, which are all products of the decomposition of wood out of contact with the air. Further it is found in vast masses, principally consisting of calcium carbonate, having their origin from sea-shells. The maintenance of life depends, as will be shown, on the small percentage of carbon dioxide which is contained in the atmosphere. Lavoisier believed that compounds of carbon were all products of life, formed under the influence of a "vital force," which was a property of the cell. It is now known that almost every constituent of the cell may be prepared from its elements in the laboratory without the aid of any "vital force" whatever. Notwithstanding its loss of strict scientific significance, the old term "organic" for a carbon compound is still in vogue, and conveniently describes a large number of bodies which are treated under the head of "organic chemistry," while the term "inorganic" is applied to the rest of the chemical world.

**Elementary Carbon.**—This burns only at a high heat. It is unaffected by the intestinal tract. This is shown by the fact that diamonds have been stolen by swallowing them, and that finely divided particles of lampblack pass unchanged and unabsorbed to the feces, coloring them black (proof that the intestinal canal does not absorb solid particles). If lampblack be eaten with a meal its appearance in the feces may be used as a demarcation line between the

<sup>1</sup> E. Bischoff: *Zeitschrift für Biologie*, 1887, Bd. 3, S. 309.

<sup>2</sup> Colassanti e Bounani: *Boll. d. R. Accad. med. di Roma*, 1896-1897; Reilly, Nolan, and Lusk: *American Journal of Physiology*, 1898, vol. i. p. 395.

<sup>3</sup> See Voit: *Hermann's Handbuch*, 1881, vi. 1, S. 79.

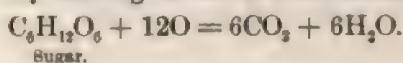
feces belonging to the period before the meal, and the period subsequent to it. Carbon unites directly with hydrogen, oxygen, and sulphur only.

**Carbon Monoxide, CO.**—This gas is a product of the incomplete combustion of carbon, is present in illuminating gas, and burns on ignition to carbon dioxide.

*Properties.*—A colorless, odorless gas. Inspired, it unites with the blood to form a carbon-monoxide hæmoglobin (Hb-(CO)). This is a very stable bright-red compound which may even be boiled without decomposing. Animals poisoned with CO die from want of oxygen, since the latter cannot displace the carbon monoxide from combination with hæmoglobin. Carbon monoxide poisoning is accompanied by diabetes<sup>1</sup> probably because of decreased power to burn sugar.

**Carbon Dioxide, CO<sub>2</sub>.**—This is the highest oxidation compound of carbon, the product of its complete combustion. It is present in the air to the extent of 0.04 per cent. It is formed in all living cells, and in higher animals is collected by the blood and brought to the lungs and skin for excretion; it is also a product of putrefaction; it gives an acid reaction to herbivorous urine. It is found dissolved in all natural waters, and is present combined in sea shells. It is found in the blood principally combined with sodium in the serum, and is likewise combined with calcium and magnesium in the bones.

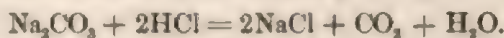
*Preparation.*—(1) By burning carbon or a carbon-containing substance,



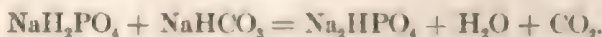
(2) By heating a carbonate,



(3) By the action of an acid on a carbonate,



In the blood, hæmoglobin and, to a less extent, serum-albumin and primary sodium phosphate act like acids. If the gases be extracted from fresh defibrinated blood in a vacuum, all the CO<sub>2</sub> is removed. If sodium carbonate be added to blood, the carbonic acid belonging to this is likewise given up in a vacuum, while a simple aqueous solution of sodium carbonate is not affected. If serum be extracted *in vacuo*, only a little more than half the carbonic acid contained in it is dissociated from combination, indicating that in the previous experiment hæmoglobin had acted like an acid. If a solution of bicarbonate of sodium (NaHCO<sub>3</sub>) be exhausted under the air-pump, just one-half of the CO<sub>2</sub> is given off, sodium carbonate (Na<sub>2</sub>CO<sub>3</sub>) remaining. In the serum more than one-half of the CO<sub>2</sub> is obtained *in vacuo*, because the serum-albumin, like the hæmoglobin, though less effectively, acts like an acid in fixing the alkali and liberating the gas. There is likewise present the action of primary phosphate on the acid carbonate,



<sup>1</sup> Straub: *Archiv für experimentelle Pathologie und Pharmacologie*, 1896, Bd. 38, S. 139.



Through these agencies the tension of carbonic acid is kept high in the blood, and its escape through the walls of the alveolar capillary is not unlike the escape of gas on uncorking a bottle of carbonated water.

After drinking a carbonated water, carbonic oxide may be detected dissolved in the urine.

*Properties.*—A colorless, odorless gas. It is poisonous, its accumulation at first stimulating and afterwards paralyzing the nervous centres. It affects the irritability—not, however, the conducting power—of the nerves. A solution of carbonic oxide in water forms carbonic acid,  $\text{H}_2\text{CO}_3$ , and from this are derived two series of salts, primary or acid salts,  $\text{MHC O}_3$ , and secondary or neutral salts,  $\text{M}_2\text{CO}_3$ .

**METABOLISM OF CARBON.**—It will be remembered that there is a union of chlorine and hydrogen on exposure to sunlight. In a similar manner the chlorophyll-containing leaf of the plant, through the medium of the energy of the sun's rays, brings the molecules of water and carbonic oxide derived from the air in such a position with regard to each other that they unite to form sugar with the elimination of oxygen (reaction on p. 501). This process is called *synthesis*—the construction of a more complicated body from simpler ones. The active or “kinetic” energy from the sun required to build up the compound is stored, becoming “potential” energy in that compound, and is liberated again in exactly the same quantity on the resolution of the substance into its original constituents. So the amount of energy liberated in the decomposition of a food in the body is exactly equal to the energy needed to build it up from its excreted constituents,<sup>1</sup> and this liberated energy appears in the body as heat, work, and electric currents.

The plant has the power of converting sugar into starch and cellulose, and likewise into fat. Further the sugar undoubtedly unites with certain nitrogen-containing bodies, and the synthesis of proteids results. Plants containing this mixture of food-stuffs become the sustaining basis of animal life. The animal devours these substances and either adds them to his body, or burns them to prevent destruction of his own substance: such are the objects of *food*. In contradistinction to synthesis in plants, animal life is said to be characterized by *analysis*, i. e., the resolution of a complicated substance into simpler ones. This classification is not entirely accurate, many exceptions occurring on both sides; for example, animals may convert sugar into fat, which is synthesis. The animal discharges its carbon partly as carbonic acid, and partly in the form of more complex organic compounds, such as urea and uric acid. Since these latter after leaving the body eventually become oxidized, and the carbon becomes completely changed to carbon dioxide, it follows that all animal carbon is finally restored to the air in the form of carbon dioxide. Thus is established the revolution of the carbon atom, made possible by the energy of the sun, between air, plants, animals, and back to air again. Burning coal, lime-kilns, volcanoes, give carbonic acid to the air. Rain water receives carbonic acid from the atmosphere, from putrefying organic matter in the soil and from the

<sup>1</sup> See Rubner, *Zeitschrift für Biologie*, 1893, Bd. 30, S. 73.

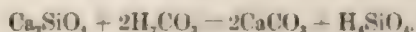
roots of trees, and ultimately much of this combines with mineral matter, or contributes to form shells in marine life.

#### SILICON, Si = 28.

Silicon is found in the ash of plants, and in traces in the cells and tissues of animals, being a constant constituent of hen's eggs. It appears in traces in the human urine, and in considerable quantity in herbivorous urine. It is especially present in hair and feathers. It does not seem to be of great importance to the life of the plant, for if corn-stalks, whose ash usually contains 20 per cent. of silica ( $\text{SiO}_2$ ), be grown in a soil free from it, the plant flourishes though only 0.7 per cent. of silica is found in the ash, this having been derived from the vessel holding the soil.

**Silicon Dioxide, or Silica,  $\text{SiO}_2$ .**—This is the oxide of the element, and is found in quartz and sand, but not in the organism.

**Silicic Acids.**—The *ortho-silicic acid* ( $\text{H}_4\text{SiO}_4$ ) is formed by the action of an acid on a metallic silicate,



This reaction takes place in the soil, and the silicic acid so obtained is soluble in water and is a *colloid*—that is to say, is of gelatinous consistence, will not crystallize, and does not osmose through vegetable and animal membranes. However, it is in this form or in the form of soluble alkaline silicate that it is probably received by the root of the plant.<sup>1</sup>

*Metasilicic acid* has the formula  $\text{H}_2\text{SiO}_3$ , while the *polysilicic acids* ( $\text{H}_2\text{SiO}_3$ ,  $\text{H}_6\text{Si}_2\text{O}_7$ , etc.) are numerous, and constitute the acid radicals of most mineral silicates. If silicic acid be evaporated and dried, it leaves a gritty residue of silica.

#### THE METALLIC ELEMENTS.

The metals in the body are the alkalis potassium and sodium, the alkaline earths calcium and magnesium, and the heavy metal iron.

#### POTASSIUM, K = 39.

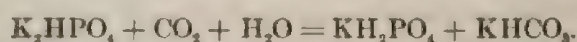
Potassium salts are found especially in all animal cells (see p. 499), and in the milk which is manufactured from the disintegration of such cells. They are found in the blood-corpuscle sometimes to the almost complete exclusion of sodium salts. Only to a small extent do they occur in the fluids of the body and in the blood plasma ( $\text{K}_2\text{O} = 0.02$  per cent. in plasma). They are excreted in the urine. Potassium salts are retained on the surface of the ground for the use of vegetation, and occur in the plant not only as inorganic but also as organic salts (tartrate, citrate, etc.).

**Potassium Chloride,  $\text{KCl}$ .**—Potassium chloride is a constant constituent of all animal cells and tissues, and may be absorbed with the food or be produced in the body after eating potassium carbonate or phosphate, since these salts may react with the sodium chloride. If fed, it is ordinarily balanced by its excretion, but if 0.1 gram be introduced into the jugular vein of a medium-sized dog, immediately paralysis of the heart ensues. It is a powerful poison for nerves and nervous centres. It melts when heated to a low red heat, and volatilizes at a higher heat.

<sup>1</sup> Bunge: *Physiologische Chemie*, 3d ed., 1894, S. 25.

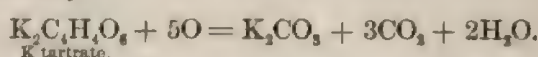


**Potassium Phosphates.**—The primary ( $\text{KH}_2\text{PO}_4$ ) and secondary ( $\text{K}_2\text{HPO}_4$ ) phosphate of potassium are the principal salts of the cells of the body, and are likewise present in the urine, and to a very small extent in the blood-plasma. They are undoubtedly intimately connected with the functional activity of protoplasm. Presence of carbonic acid causes the conversion of the secondary phosphate into the primary salt, and this occurs in the blood-corpuscle as well as in the plasma :



Primary acid phosphate of potassium contributes to the acid reaction of the urine, though in presence of sodium chloride there is a tendency to the formation of primary sodium phosphate and potassium chloride. It is the cause of the acid reaction in muscle in *rigor mortis* (see p. 546).

**Potassium Carbonates.**—The primary and secondary carbonates exist in the body only in trifling quantities. They may be produced as above described by the action of carbonic acid on the phosphates, they may be ingested with the food, or they may result in the body from the combustion of an organic salt of potassium, according to the same reaction as would take place by burning it in the laboratory,



Feeding potassium carbonate or an organic salt of potassium makes the urine alkaline owing to the excretion of potassium carbonate.

Potassium salts are poisonous if introduced into the blood in too large quantities. In concentrated solutions in the stomach they produce *gastritis*, even with quickly fatal results.<sup>1</sup>

Zuntz believes that potassium is combined with hæmoglobin in the blood-corpuscle, and may be dissociated from it by the action of carbonic oxide.<sup>2</sup>

**POTASSIUM IN THE BODY.**—The various salts of potassium are received with the food in the manner described; the phosphate may be retained for new tissue, but the other salts are removed in the urine. They are all quite completely absorbed in the intestinal tract. In starvation, or in fever, where there is high tissue-metabolism, the body suffers greater loss of the potassium phosphate-containing tissue than it does of the sodium-rich blood, and potassium exceeds sodium in the urine (reverse of the usual proportion); also milk, which is prepared from tissue, contains more potassium than sodium. Bunge<sup>3</sup> has noted an important influence of potassium salts. If a potassium salt be in solution together with sodium chloride, the two partially react on each other, with formation of potassium chloride. If now potassium carbonate, for example, be eaten, the same reaction occurs in the body,



The kidney has the power of removing soluble substances which do not belong to the blood or are present in it to excess, and consequently the two salts

<sup>1</sup> Bunge: *Physiologische Chemie*, 3d ed., 1894, S. 136.

<sup>2</sup> A. Loewy und N. Zuntz: *Pflüger's Archiv*, 1894, Bd. 58, S. 522.

<sup>3</sup> *Op. cit.*, S. 108.

formed as above are excreted. Hence potassium carbonate has caused a direct loss of sodium and chlorine. For this reason, if potatoes and vegetables very rich in potassium salts are eaten, sodium chloride must be added to the food to compensate for the loss. Nations living on rice do not need salt, for here the potassium content is low. Tribes living solely on meat or fish do not use salt, but care is taken that the animals slaughtered for food shall not lose the blood, rich in sodium salts, and strips of meat dipped in blood are, by some races, considered a delicacy.<sup>1</sup>

SODIUM, Na = 23.

Sodium salts belong particularly to the fluids of the body (see p. 504), blood-plasma containing 0.4 per cent. calculated to Na<sub>2</sub>O.

Sodium chloride, NaCl, is found in all the fluids of the body. It is found in blood and lymph to an extent of about 0.65 per cent., in the saliva, gastric juice, milk, sweat, urine, etc. Sodium chloride, like potassium chloride, melts at a low red heat, hence the fluids of the body yield a fluid ash, with the single exception of milk, which contains a high percentage of infusible calcium phosphate. Sodium chloride is very readily soluble. In the blood it acts as a solvent on serum-globulin and other proteids, and its inert presence in proper concentration affords a medium in which the functional activity of cells and tissues is maintained. (For "physiological salt-solution" see p. 504.) From sodium chloride the hydrochloric acid of the gastric juice is prepared (see p. 508); it is also a necessary addition to every food where potassium salts are in great preponderance (see p. 520), but it is taken by most races in amounts far above these physiological necessities.

If a mixture of necessary food-stuffs—proteid, fats, starch, salts, and water—in proper proportion, but without flavor, be set before a dog, he will starve rather than touch it. A man will attempt its digestion, but the permanent support of life is impossible. A food to support life must be a well-tasting mixture of food-stuffs, for, through the action of the flavor on the mucous membrane of the mouth and stomach there is established reflexly a nervous influence causing a proper flow of the various digestive juices. Hence salt, pepper, mustard, beer, wine, and other condiments are taken with the food. What the change is, when a substance acts on the taste-buds of the tongue, for example, starting a motion such as is afterwards interpreted in the brain as flavor, is unknown. Chemical constitution gives no hint how a body will taste or smell.

In carnivora every trace of sodium chloride is absorbed by the villi from the intestinal tract. This is a proof that absorption does not depend on simple physical osmosis, in which case the intestinal contents would tend to have the same percentage composition as the blood, but upon the selective capacity of the exposed protoplasm of the villi. Sodium chloride is the principal solid constituent of sweat and of tears. Usually, however, it is lost to the body through the urine, of whose ash it forms the chief constituent. The quantity of salt in the urine is decreased during gastric digestion (see p. 508). Sodium chloride if fed is largely excreted in the urine within the following twenty-four hours.<sup>2</sup> Experiments of abstention from salt have never been carried

<sup>1</sup> Bunge : *Op. cit.*, S. 116.

<sup>2</sup> Straub : *Zeitschrift für Biologie*, 1899, Bd. 37, S. 483.



so far as to produce vital disturbances, but the physiological minimum is probably very low. A dog weighing 35 kilograms may live on 0.6 gram of salt daily.<sup>1</sup> Sodium chloride, fed, produces of itself alone an increase of water in the urine. If sodium chloride or other salts act as diuretics and remove water from the tissues, an increase in proteid metabolism results. Simple withdrawal of part of the water from the tissues raises the proteid metabolism but does not affect the amount of fat burned.<sup>2</sup>

**Sodium sulphate**,  $\text{Na}_2\text{SO}_4$ , called "Glauber's salt," is found together with potassium sulphate in the urine in the condition of preformed sulphuric acid (see p. 507). If fed, it reappears in the urine. It acts on the epithelial cells of the intestines, preventing the absorption of water, consequently causing diarrhœa. Other laxatives act in the same way.

**Sodium Phosphates.**—The primary ( $\text{NaH}_2\text{PO}_4$ ) and the secondary ( $\text{Na}_2\text{HPO}_4$ ) salts are found to a small extent in the blood-plasma and other fluids, and in the urine. As with the potassium phosphates, carbonic oxide acts when in certain excess to convert the secondary phosphate into  $\text{NaH}_2\text{PO}_4$  and  $\text{NaHCO}_3$ . These two, however, may react on one another to drive off carbonic acid (see p. 517). Carnivorous urine owes its acid reaction principally to primary sodium phosphate. If a mixture of  $\text{NaH}_2\text{PO}_4$  and  $\text{Na}_2\text{HPO}_4$  be permitted to diffuse through membranes, the  $\text{NaH}_2\text{PO}_4$  passes through in greater quantity, and this process may take place in the kidney.<sup>3</sup> Secondary sodium phosphate dissolves uric acid on warming, forming sodium acid urate and primary phosphate, which solution reacts acid (Voit). Urine standing in the cold precipitates uric acid with the formation of secondary phosphates, while the reverse reaction with return of original acidity takes place on warming the urine.

**Sodium Carbonates.**—Of these there are two, the primary,  $\text{NaHCO}_3$ , and the neutral,  $\text{Na}_2\text{CO}_3$ . The organism owes its alkaline reaction, and also its power of combining with carbonic acid, almost entirely to sodium carbonate. Saliva, pancreatic and intestinal juice are strongly alkaline with sodium carbonate, as are also blood, lymph, and other fluids. If the organism be acidified, by feeding acid to a rabbit, for example, death occurs even before complete loss of the blood's alkalinity, while venous injections of sodium carbonate at the proper time restore the animal. Carbonic oxide cannot be removed from the tissues in the acidified blood. Sodium carbonate treated with carbonic acid becomes acid sodium carbonate, and this change is effected in the internal respiration, where the cells give  $\text{CO}_2$  to the blood. Treated with acids, both carbonates liberate carbonic oxide—a reaction which takes place in the blood (see p. 517). Bunge suggests that the acid chyme of the stomach, into whose finest particles the alkaline intestinal juice diffuses, is especially penetrable by the latter's enzymes, because liberated carbonic oxide has separated the particles of chyme from each other. The same principle would hold true of a morsel well mixed with saliva, which, as is well known, is more easily penetrable by

<sup>1</sup> Voit: *Hermann's Handbuch*, 1881, vi. 1, S. 367.

<sup>2</sup> Straub: *Zeitschrift für Biologie*, 1899, Bd. 38, S. 537.

<sup>3</sup> Soubiranski: *Archiv für exper. Pathologie und Pharmacologie*, 1895, Bd. 35, S. 178.

gastric juice than one not so mixed. Sodium carbonate may be obtained for the body either directly from the food by absorption, or indirectly through combustion of sodium organic salts. Ingested in sufficiently large quantities, it makes the urine alkaline.

Sodium salts are undoubtedly united with serum-albumin in the plasma, forming a combination which may be dissociated by carbonic oxide.

Sodium gives a yellow coloration to a colorless flame, and a distinctive bright line in the yellow of the spectroscope.

**SODIUM IN THE BODY.**—This subject has been discussed under the different salts, and likewise under potassium and hydrochloric acid; repetition here is therefore needless.

#### AMMONIUM, $\text{NH}_4$ .

**Ammonia**,  $\text{NH}_3$ , has already been described (p. 511).

**Sodium-Ammonium Phosphate**,  $\text{NaNH}_4\text{HPO}_4$ , is an insoluble salt formed in the urine during ammoniacal fermentation.

**Ammonium Carbonate**,  $(\text{NH}_4)_2\text{CO}_3$ , is formed by the union of carbonic oxide and ammonia in the presence of water, and is therefore a usual product of putrefaction. If introduced into the blood, it is converted into urea by the liver. In *uremia* urea passes from the blood into the stomach and is there converted into ammonium carbonate, which produces vomiting through irritation of the mucous membrane. (See further discussion under Carbamic Acid and Urea.)

#### CALCIUM, $\text{Ca} = 40$ .

Calcium is by far the most abundant metallic element in the body, and, as has been found in the dog, 99.5 per cent. belongs to the composition of the bones.<sup>1</sup> Outside the bones it occurs most abundantly in blood-plasma. It is found in all the cells and fluids of the body, probably loosely combined with proteid. Calcium is always accompanied by magnesium.

**Calcium Chloride**,  $\text{CaCl}_2$ , is found in small quantities in the bones.

**Calcium Fluoride**,  $\text{CaF}_2$ , a salt insoluble in water, is found in bone, dentine, and enamel (see p. 510).

**Calcium Sulphate**,  $\text{CaSO}_4$ , is found in small quantities in bones and rarely as part of the sediment in strongly acid urine.

**Calcium Phosphates.**—Of these there are three—primary,  $\text{CaH}_4(\text{PO}_4)_2$ , secondary,  $\text{CaHPO}_4$ , and tertiary,  $\text{Ca}_3(\text{PO}_4)_2$ . The tertiary phosphate is insoluble in water, the secondary only very slightly soluble, but the primary salt is soluble. The tertiary and secondary phosphates are insoluble in alkali, but soluble in mineral acids and in acetic acid. The tertiary phosphate forms the largest mineral constituent of the bones (83.89 per cent., Zalesky) and of dentine and enamel. Tertiary phosphate of calcium likewise occurs in the blood; how it is held in solution it is difficult to say, though it is probably loosely combined with proteid. In a similar way it is combined with the protoplasm of the cell. It is largely found in the ash of milk, having been in previous chemical combination with casein. Tertiary phosphate of calcium is continu-

<sup>1</sup> Heuss: *Zeitschrift für Biologie*, 1876, Bd. 12, S. 165.



ously excreted into the intestinal tract. It is present in the acid gastric juice, but only in traces in the alkaline saliva, pancreatic juice, and in the nearly neutral bile. Tertiary phosphates never occur in the urine, except as a sediment after the urine has attained an alkaline reaction, being formed from the acid phosphates. In carnivorous urine the calcium present occurs as primary and secondary phosphate, the solution of the latter being aided by the primary alkali phosphate and sodium chloride. Occasionally a coat is noticed on the surface of the urine, an appearance once thought to be a sign of pregnancy. This coat is now known to consist chiefly of secondary phosphate of calcium, which may crystallize out on the urine becoming alkaline. Calcium does not occur as phosphate in an alkaline urine (see p. 515).

**Calcium Carbonates.**—Of these there are two, the primary or acid,  $\text{CaH}_2(\text{CO}_3)_2$ , and the secondary or neutral carbonate,  $\text{CaCO}_3$ . Neutral calcium carbonate is the substance of which sea shells, coral, egg-shell, and otoliths consist. It is found in the ash of bones to the extent of 13.032 per cent. (Zalesky). Apatite is a mineral having the formula  $\text{Ca}_{10}\text{F}_2(\text{PO}_4)_6$ , and Hoppe-Seyler, using Zalesky's figures, believes that bone has a composition represented by  $\text{Ca}_{10}\text{CO}_3(\text{PO}_4)_6$ , or  $3\text{Ca}_3(\text{PO}_4)_2\cdot\text{CaCO}_3$ , in which  $\text{CO}_3$  has the position of  $\text{F}_2$  in apatite. In the wasting of the mineral matter of bones in *osteomalacia* this formula of composition remains constant,<sup>1</sup> one molecule of calcium carbonate always being removed for every three molecules of the phosphate. Neutral calcium carbonate is insoluble in water or alkali, but dissolves in water containing carbonic oxide to form the soluble acid carbonate,  $\text{CaH}_2(\text{CO}_3)_2$ . This is found in blood and lymph, and in minute quantities in all the tissues. It is found in herbivorous urine, which contains carbonic acid in excess, but it is soon deposited as neutral carbonate as the carbonic oxide diffuses into the air. It occurs in all alkaline and neutral urines, though to a less extent than calcium phosphate in acid urines. It is found in pancreatic juice and in the saliva, from which latter is derived the calcic carbonate which, mixed with bacteria and other organic matter, is deposited as *tartar* on the teeth.

The ferment rennet does not act in the absence of calcium salts. The coagulation of the blood requires the presence of calcium salts.<sup>2</sup> If ten parts of blood be drawn into one part of a 1 per cent. solution of potassium oxalate, thus precipitating the calcium, no coagulation takes place, but on the addition of calcium chloride a typical fibrin forms. According to Hammarsten,<sup>3</sup> calcium is only necessary in the formation of the ferment. He has prepared fibrin containing only a trace (0.007 per cent.) of calcium. A solution of sodium oxalate passed through a beating excised heart causes it to cease beating,<sup>4</sup> and nerves and muscles lose their irritability when calcium salts are abstracted from them with sodium oxalate.<sup>5</sup> These facts illustrate

<sup>1</sup> M. Levy: *Zeitschrift für physiologische Chemie*, 1894, Bd. 19, S. 239.

<sup>2</sup> Arthus et Paget: *Archives de Physiologie*, 1890, p. 739.

<sup>3</sup> Hammarsten: *Zeitschrift für physiologische Chemie*, 1899, Bd. 28, S. 90.

<sup>4</sup> Howell and Cooke: *Journal of Physiology*, 1893, vol. 14, p. 219, note.

<sup>5</sup> Howell: *Ibid.*, 1894, vol. 16, p. 476.

the intimate relation between calcium salts and the functional activity of protoplasm. Howell<sup>1</sup> believes that calcium salts furnish the primary stimulus for the contraction of the heart.

**CALCIUM IN THE BODY.**—Calcium salts are especially needed in childhood for the growth of the bones. It has been estimated that the human suckling requires 0.32 gram CaO daily, and in the milk for that time is contained 0.55 gram to 2.37 grams, so that there may easily be lack of CaO when absorption is unfavorable. In children with rickets the bones contain too little calcium, and are abnormally weak and flexible. This same condition may be reproduced in young growing dogs by feeding them entirely on meat and fat, which contain too little calcium for proper skeletal development.<sup>2</sup> Such dogs grow rapidly in size, especially around the thorax, while the pelvis remains ludicrously small, the extremities become bent and finally incapable of supporting the weight of the body. A puppy of the same litter fed on the same food but with the addition of bones grows normally. In certain cases even when children are fed with sufficient calcium they still have the rickets. This might be due to a lack of ability to absorb the salts, but this Rüdell<sup>3</sup> has disproved. To a child having rickets he administered a calcium salt, and confirmed its absorption by the increase in the calcium contents of the urine, the result being the same as with a normal child. (Example: Normal day, 0.0196 gram CaO in urine; after feeding 1.4 grams CaO dissolved in acetic acid the amount in the urine rises to 0.0396 gram for the twenty-four hours.) Rüdell therefore concludes that the cause of rickets may be in a local change of the bones themselves, whereby calcium salts are not deposited in the normal manner.

In *osteomalacia* there occurs a solution of the salts of the bones in adult life, called softening of the bones. In *osteoporosis*, which is a simple atrophy of the bones, similar effects are produced. Voit<sup>4</sup> fed a pigeon for a year on washed wheat and distilled water, at the end of which time the pigeon apparently did not differ from the normal bird. A few months later a wing was broken, and the autopsy discovered osteoporosis in high degree, the skull being especially attacked. Weiske<sup>5</sup> has shown that rabbits ultimately die when fed on oats which are poor in calcium; the oats yield an acid ash and produce an acid urine. On autopsy osteoporosis is found. This does not take place when calcium carbonate is added to the food. Whether the loss of salts to the bone is due to a normal metabolism, or to solution due to the production of acids in the metabolism of proteid, is an unanswered problem (see pp. 506, 511) the discussion of which lack of space forbids.<sup>6</sup> In such experiments as the above, the percentage of ash is always diminished, while the percentage of organic matter always rises, whereas the actual percentage composition of the ash itself remains the same. This is a strong argument in favor of the view that bone is a mineral of definite chemical composition. The mineral matter of bone is believed by some to be loosely combined with the organic material, principally ossein, but of this there is no proof.

The exact amount of calcium salt necessary to keep up the supply in the adult body is unknown, but it must be exceedingly small. A dog of 3.8 kilograms eating with his food 0.043 gram CaO maintains his calcium equilibrium (Heiss).

Regarding the absorption of calcium salts, it has long been questioned whether inorganic salts can be absorbed, since, it was argued, insoluble

<sup>1</sup> *American Journal of Physiology*, 1898, vol. 2, p. 47.

<sup>2</sup> E. Voit: *Zeitschrift für Biologie*, 1880, Bd. 16, S. 70.

<sup>3</sup> *Archiv für exper. Pathologie und Pharmacologie* 1893, Bd. 33, S. 90.

<sup>4</sup> *Hermann's Handbuch*, 1881, vi. 1, S. 379.

<sup>5</sup> *Zeitschrift für Biologie*, 1894, Bd. 31, S. 421.

<sup>6</sup> See Weiske, *Loc. cit.*: Bunge, *Physiologische Chemie*, 3d ed., 1894, S. 104; V. Noorden, *Pathologie der Stoffwechsels*, 1893, S. 48 and 413.



phosphate would immediately be precipitated in the blood. It has, however, been conclusively shown that such salts when eaten produce an increase in the calcium of the urine<sup>1</sup> and it is known that blood has a special capability for carrying calcium phosphate. Calcium carbonate and chloride are capable of absorption, while absorption of the phosphate may be considered as still in doubt. If calcium chloride be given, a little of the calcium appears in the urine, and all of the chlorine, this being due to the conversion in the intestine of calcium chloride into calcium carbonate and sodium chloride, which latter is completely absorbed. Organic salts of calcium such as the acetate are absorbable, as are probably proteid combinations with calcium such as casein. Milk and egg-yolk are the foods richest in calcium salts, cow's milk containing more calcium to the liter than does lime-water.<sup>2</sup>

The excretion of calcium takes place in major part as triple phosphate from the wall of the small intestine,<sup>3</sup> in minor part through the urine (for the latter see pp. 515 and 524). It is excreted during starvation, and is the principal inorganic constituent of starvation feces (Voit). The secretions of the intestines, according to Fr. Müller,<sup>4</sup> hardly contain enough calcium to account for that found in the feces, so that it is probably excreted by the epithelial cells of the villus. In starvation the source of excreted calcium is principally from the breaking down of tissue, but partially from the metabolism of the bones. The excretion is never large. On subcutaneous injection of small amounts of calcium acetate in dogs,<sup>5</sup> the calcium excretion may be raised for several days. On venous injection of 0.8 gram CaO as acetate, after one hour but 0.3 gram could be found above the normal in the blood, and analysis of the liver, kidney, spleen, and intestinal wall failed to reveal more than the usual minimal amounts of calcium. As it is never rapidly excreted, it must have been temporarily deposited in some unknown part of the body.

#### STRONTIUM, Sr = 87.5.

Cremer<sup>6</sup> has shown, on adding strontium phosphate to almost calcium-free food of young growing dogs, that the strontium line could be detected in the subsequent spectral analysis of their bones. Weiske,<sup>7</sup> on feeding young rabbits with food nearly free from calcium, and with addition of strontium carbonate, found the ash in some of the bones to contain, in the place of CaO, as high as 4.09 per cent. of SrO. In both of the above experiments the skeleton remained very undeveloped in comparison with the normal, so that strontium cannot be considered a physiological substitute for calcium.

<sup>1</sup> Rüdel, *Op. cit.*, S. 79.

<sup>2</sup> Bunge: *Physiologische Chemie*, 3d ed., 1894, S. 101.

<sup>3</sup> Voit F.: *Zeitschrift für Biologie*, 1893, Bd. 29, S. 325.

<sup>4</sup> *Zeitschrift für Biologie*, 1894, Bd. 20, S. 350.

<sup>5</sup> Rey: *Archiv für exper. Pathologie und Pharmakologie*, 1895, Bd. 35, S. 298.

<sup>6</sup> *Sitzungsberichte der Gesellschaft für Morphologie und Physiologie in München*, 1891, Bd. 7, S. 124.

<sup>7</sup> *Zeitschrift für Biologie*, 1894, Bd. 31, S. 437.

MAGNESIUM,  $\text{Mg} = 24.3$ .

This is the second in importance of the alkaline earths. It is present wherever calcium is found, but in comparison with calcium it has been little investigated. It occurs principally as phosphate, but is found as carbonate in herbivorous urine. Of the total quantity of magnesium in the dog, Heiss found that 71 per cent. belonged to the bones. It is found decidedly predominating over calcium in muscle, but is less in quantity than calcium in the blood.

**Magnesium Phosphates.**—Magnesium tertiary phosphate,  $\text{Mg}_3(\text{PO}_4)_2$ , is found in the ash of bones to the extent of about 1 per cent., is present in blood and especially in muscle, probably in combination with proteid, and contributes to the functional activity of protoplasm. It is continuously excreted by the walls of the intestinal canal. The primary and secondary phosphates of magnesium are found in carnivorous urine, solution of the latter being aided by the presence of primary alkali phosphate and sodium chloride. Tertiary phosphate of magnesium is insoluble in water, the secondary very slightly so, the primary quite soluble; but all are soluble in acids. In the ammoniacal fermentation of the urine, *ammonium magnesium phosphate*,  $\text{MgNH}_4\text{PO}_4$ , is precipitated as a fine crystalline powder insoluble in alkalies. Whenever this fermentation takes place, whether in the bladder or, by similar reaction, in the intestines (herbivora especially), stones are formed.<sup>1</sup>

**Magnesium Carbonates.**—The neutral carbonate,  $\text{MgCO}_3$ , is insoluble in water, but soluble in water containing carbonic oxide, forming secondary or acid carbonate,  $\text{MgH}_2(\text{CO}_3)_2$ . This latter occurs in herbivorous urine.

**MAGNESIUM IN THE BODY.**—Considerations regarding the absorption of calcium apply likewise to magnesium. It is absorbed by the intestine as inorganic and probably as organic combinations. If growing rabbits be fed on a diet poor in calcium salts, but containing magnesium carbonate, the bones may be brought to contain double the normal quantity of magnesium, but the skeletal development remains far behind that of a normal rabbit, and therefore magnesium can in no sense be considered a substitute for calcium.<sup>2</sup> The magnesium salts, whether phosphate or carbonate, being more soluble than the calcium salts, occur in the urine in greater abundance. Indeed, in carnivorous urine the major part of excreted magnesium is found in the urine, the balance being given off through the intestinal wall to the feces. In starvation the source of the excreted magnesium is from the bones, and especially from destruction of its combination in proteid metabolism.

IRON,  $\text{Fe} = 56$ .

This is the one heavy metal which is an absolute necessity for the organism. About three grams occur in the average man. It has been demonstrated of certain bacteria that they will not develop in the absence of iron.

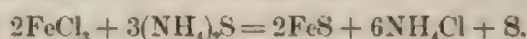
<sup>1</sup> For example in man see C. Th. Mörner: *Zeitschrift für physiologische Chemie*, 1897, Bd. 22, 8. 522.

<sup>2</sup> Weiske: *Zeitschrift für Biologie*, 1894, Bd. 31, S. 437.



and this is believed to be true of all protoplasm. Iron is found throughout the body, and is especially an ingredient of hæmoglobin (0.4 per cent.), which carries oxygen to the tissues. It is found deposited in the liver and the spleen as ferratin, hepatin, and other less investigated organic compounds. It is found in muscle washed free from blood. Iron appears in urine and in milk as organic compounds, and in the bile, gastric juice, and intestines as phosphate, in the feces as sulphide. Iron occurs in two forms, the ferro- and ferri-compounds, in which it has respectively two and three bonds.

**Ferrosulphide, FeS.**—This is found in the feces and is the product of the action of sulphuretted hydrogen or alkaline sulphide on both inorganic iron and likewise, more slowly, on organic iron-containing compounds (ferratin, hæmatogen, etc.). Ammonium sulphide acts in a similar manner, and, in all cases, ferric salts are reduced to ferrous:



Ferric chloride.

**Ferric Phosphate, FePO<sub>4</sub>.**—This is found in the gastric juice, bile, and probably in the intestinal juice;<sup>1</sup> it is not, as many have believed, given off by the epithelia of the intestines. It is soluble in mineral acids, but insoluble in water, alkalies, or acetic acid.

**IRON IN THE BODY.**—The amount of iron in the urine is very small, amounting daily in a large starving dog to 0.0013–0.0049 gram.<sup>2</sup> Feeding iron compounds does not increase the amount of iron in the urine. Forster<sup>3</sup> fed a dog of 26 kilograms for thirty-eight days with washed meat containing 0.93 grams of iron, and in the feces were found 3.59 grams belonging to the same period. Here there was a loss of 2.66 grams<sup>4</sup> of iron from the body, and the necessity of iron as a food was established.

Concerning the method and the amount of iron-absorption, considerable difficulty has been encountered owing to the fact that both absorptive and secretive organs lie in the intestinal canal. On feeding a dog for thirteen days with meat containing 0.180 gram Fe, there were found in urine and feces for the same time 0.1765 gram Fe; then to the same food for a similar length of time were added 0.441 gram Fe (as sulphate), making in all 0.636 gram Fe, and of this 0.6084 gram were recovered in the excreta.<sup>5</sup> This experiment proves only that such absorption as may take place is pretty nearly balanced by the excretion. After eating blood the feces are found to contain much hæmatin, and it has been thought that iron could not be absorbed in that way, but Abderhalden<sup>6</sup> has recently shown that there can be a small amount of iron absorption after feeding either hæmoglobin or hæmatin. Bunge has sought for one of the antecedents of hæmoglobin in egg-yolk, and has described it as an iron-containing nucleo-albumin, which he names hæmatogen. That and similar nucleo-albumins existing in plants he conceives to be the source of absorbable iron, while inorganic salts of iron aid only indirectly by forming iron sulphide, thus preventing the same formation from organic iron (see above). Small amounts of absorbable iron are found in all the ordinary cereal foods.<sup>7</sup> Marfori<sup>8</sup> has

<sup>1</sup> Macallum: *Journal of Physiology*, 1894, vol. 15, p. 288.

<sup>2</sup> Forster: *Zeitschrift für Biologie*, 1873, Bd. 9, S. 297.

<sup>3</sup> *Loc. cit.*

<sup>4</sup> This figure is probably too high, but the principle itself is fundamental. See Voit, *Hermann's Handbook*, 1881, vi. 1, S. 335.

<sup>5</sup> Hamburger: *Zeitschrift für physiologische Chemie*, 1878, Bd. 2, S. 191.

<sup>6</sup> *Zeitschrift für Biologie*, 1900, Bd. 39, S. 487.

<sup>7</sup> Bunge: *Zeitschrift für physiologische Chemie*, 1898, Bd. 25, S. 36.

<sup>8</sup> *Archiv für exper. Pathologie und Pharmacologie*, 1891, Bd. 29, S. 212.

prepared a substance from proteid and iron salts, called ferratin, which contains 4 to 8 per cent. of iron: it is a compound unaffected by gastric juice or by boiling: it is soluble in the alkaline intestine, where it is but slowly affected by alkaline sulphide. Now this same ferratin is found in the body itself, especially in the liver,<sup>1</sup> although not the only iron-containing substance of the liver.<sup>2</sup> If ferratin be fed, the quantity of it increases in the liver. If a dog be fed on milk, which is always poor in iron, and he be bled from time to time, the ferratin disappears from the liver, being used for the formation of new red blood-corpuscles.<sup>3</sup> Such a liver does not change color when placed in dilute ammonium sulphide, while one containing ferratin or other iron compounds gradually turns black from iron sulphide. If milk containing ferratin be fed, the ferratin may be deposited in the liver for the use of the blood. As it is not decomposed by boiling, ferratin is found in the usual cooked meat. Concerning the influence of inorganic salts, Schmiedeberg agrees with Bunge that the formation of iron sulphide protects the ferratin from attack.

The insolubility of iron salts in alkaline solutions has raised the question of their absorption by the blood. If inorganic iron salts be injected into a vein, the iron reappears chiefly in the intestines, with only 3 to 4 per cent. in the urine (Jakobj): in too great quantities they have powerful toxic properties. Gottlieb<sup>4</sup> administered 0.1 gram of iron as sodium iron tartrate subcutaneously to a dog during a period of nine days; twenty-eight days after the first injection 0.0969 gram Fe had been removed in the excreta over and above the normal excretion calculated for the same time. It was shown that this iron was especially stored in the liver. It may be argued that such iron, being foreign to the organism, was deposited in the liver and gradually excreted as other heavy metals, mercury, copper, lead, would be. Kunkel<sup>5</sup> fed mice and to the food of half their number added a solution of oxychloride of iron ( $\text{FeCl}_3 \cdot 4\text{Fe}(\text{OH})_3$ , liquor ferri oxychlorati) in the livers of those fed with iron, iron was present to a greater extent than in the others; but here, again, the surplus can be attributed to the sulphide-forming protective power of the added salts, which Kunkel admits, though maintaining the contrary ground. The proof of the absorption of inorganic salts emanates from Macallum,<sup>6</sup> who showed, after feeding chloride, phosphate, and sulphate to guinea-pigs, that the epithelial cells and the subepithelial leucocytes of the intestines gave a strong microchemical reaction for iron with ammonium sulphide. With small doses this was observed only near the pylorus, for iron is soon precipitated by the alkali of the intestines, but where the iron salt was in sufficient quantity to neutralize the intestinal alkali it could be absorbed the whole length of the small intestine. Whether inorganic iron unites with proteid before absorption or not is unknown. According to Swirski, the absorbed iron compounds pass into the lymph or into the blood of the portal vein. In the latter they are taken up by the leucocytes (phagocytes) and carried to the liver. Fasting guinea-pigs which have been prevented by muzzling from eating their feces and thus deprived of even a small quantity of iron, are more susceptible to disease than the same unmuzzled animals. The iron-containing phagocytes are believed to destroy bacterial poisons.

Regarding the transformation of iron compounds after absorption into hæmoglobin, little is known except that the necessary synthesis takes place in the spleen, in the bone-marrow, and probably in the liver. On the destruction of red blood-corpuscles, proteid bodies holding iron in combination are deposited in the cells of the liver, spleen, bone-marrow, and kidney,<sup>7</sup> this being noticeable in pernicious anemia. On the production of

<sup>1</sup> Marfori, *loc. cit.*, and Schmiedeberg, *Archiv für exper. Pathologie und Pharmacologie*, 1894, Bd. 33, S. 101.

<sup>2</sup> Vay: *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, S. 398.

<sup>3</sup> Schmiedeberg, *Op. cit.*, S. 110.

<sup>4</sup> *Zeitschrift für physiologische Chemie*, 1891, Bd. 15, S. 371.

<sup>5</sup> *Pflüger's Archiv*, 1891, Bd. 50, S. 11.

<sup>6</sup> Swirski: *Ibid.*, 1899, Bd. 74, S. 466; *Journal of Physiology*, 1894, vol. 16, p. 268.

<sup>7</sup> Schurig: *Archiv für exper. Pathologie und Pharmacologie*, 1898, Bd. 41, S. 29.



icterus with arseniuretted hydrogen, similar iron compounds are noted in the liver, being cleavage products of hæmoglobin in its transformation to biliary coloring matter. The amount of iron normally excreted from the body is far less than the corresponding biliary coloring matter (see Hæmochromogen), showing that the rest of the iron is retained for further use in constructing new hæmoglobin. After extirpation of the spleen the amount of coloring matter in the bile may decrease more than one-half, indicating that biliary coloring matter is normally formed in the spleen through the destruction of hæmoglobin, and is carried by the portal vein to the liver.<sup>1</sup>

Iron is excreted as phosphate in the gastric juice, in bile (in considerable quantity), and, according to Macallum,<sup>2</sup> in the intestinal juice. In the urine it is present as an unknown organic compound.

A newborn child or animal has, proportionately to its weight, far more iron than at any other time of its life. This iron is lost only very slowly, hence the very small quantity of iron in the milk answers all necessities. The other salts of the milk are in the same proportion to one another as are the salts in the newborn animal.

Tables representing generally accepted analyses of the mineral constituents of the more important fluids and cells of the body are subjoined. Only very pronounced differences are to be taken into consideration in drawing conclusions, for analyses of animals of different species, or of the same species, or even of the same animal at different times, show wide variations. The tables represent parts in 1000 of fresh substance:

## I.

	K <sub>2</sub> SO <sub>4</sub>	KCl	NaCl	Na <sub>2</sub> CO <sub>3</sub>	CaCO <sub>3</sub>	Ca <sub>3</sub> PO <sub>4</sub>	MgCO <sub>3</sub>	Mg <sub>2</sub> (PO <sub>4</sub> ) <sub>3</sub>	FePO <sub>4</sub>
Saliva <sup>3</sup> (dog) . . .	0.209	0.940	1.546	0.940	0.160	0.113			
Pancreas <sup>4</sup> (dog) . . .		0.93	2.53	3.90(Na <sub>2</sub> O)		0.07		0.01	
Gastric juice <sup>5</sup> (dog) . . .		1.125	2.567		0.624(CaO <sub>2</sub> )	1.729	0.01(MgO)	0.226	0.082
Fresh bile <sup>6</sup> (dog) . . .	0.022		0.185	0.066	0.080	0.039	0.007(MgO)		0.021

## II.

	K <sub>2</sub> O	Na <sub>2</sub> O	CaO	MgO	Fe <sub>2</sub> O <sub>3</sub>	Cl	P <sub>2</sub> O <sub>5</sub>
Blood serum <sup>7</sup> (dog) . . .	0.202	4.341	0.176	0.041	0.01	3.961	0.489
Blood corpuscles <sup>8</sup> (pig) . . .	5.543	0	0	0.158		1.504	2.067
Blood serum <sup>9</sup> (pig) . . .	0.273	4.272	0.136	0.038		3.611	0.188
Muscle <sup>10</sup> (ox) . . . . .	4.654	0.770	0.086	0.412	0.057	0.672	4.644
Milk <sup>10</sup> (cow) . . . . .	1.67	1.05	1.51	0.20	0.003	1.86	1.60

<sup>1</sup> Pugliese: *Archiv für Physiologie*, 1899, S. 80.

<sup>2</sup> *Op. cit.*, p. 278.

<sup>3</sup> Herter: Hoppe-Seyler's *Physiologische Chemie*, S. 192.

<sup>4</sup> Krüger: Quoted by Halliburton, *Chemistry, Physiological and Pathological*, p. 656.

<sup>5</sup> Bidder and Schmidt: Quoted by Halliburton, *Op. cit.*, p. 638.

<sup>6</sup> Hoppe-Seyler: *Physiologische Chemie*, S. 302.

<sup>7</sup> Runge: *Ibid.*, 3d ed., S. 265.

<sup>8</sup> *Op. cit.*, S. 222. For other similar blood analyses, see Abderhalden, *Zeitschrift für physiologische Chemie*, 1898, Bd. 25, S. 65.

<sup>9</sup> Runge: *Ibid.*, 1885, Bd. 9, S. 60.

<sup>10</sup> Bunge: *Physiologische Chemie*, 3d ed., S. 100.

## THE CHEMISTRY OF THE COMPOUNDS OF CARBON.

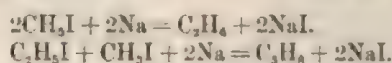
## DERIVATIVES OF METHANE.

The complicated structure and the great variety of the compounds of carbon are due to the fact that carbon-atoms have a greater power for union with one another than have the atoms of other elements.

**Saturated Hydrocarbons or Paraffins** (formula,  $C_nH_{2n+2}$ ).—

Methane, $CH_4$ , gas.	Pentane, $C_5H_{12}$ , liquid at $38^\circ$ .
Ethane, $C_2H_6$ , “	Hexane, $C_6H_{14}$ , “ $71^\circ$ .
Propane, $C_3H_8$ , “	Heptane, $C_7H_{16}$ , “ $98^\circ$ .
Butane, $C_4H_{10}$ , “	etc.

These are the constituents of petroleum and natural gas, and are formed by the action of low heat on coal under pressure in the absence of oxygen, and are probably derived from fossil animal fat, since it has been shown that the paraffins may be obtained in large quantity by heating fish oil at a pressure of ten atmospheres.<sup>1</sup> The paraffins may all be formed synthetically from methane by the action of sodium on halogen compounds of the group:



This may be continued to form a theoretically endless number of compounds. Paraffins are notably resistant to chemical reagents, not being affected by either concentrated nitric or sulphuric acids. *Vaseline* contains a mixture of paraffins melting between  $30^\circ$  and  $40^\circ$ . By *massage* vaseline may be absorbed by the skin, through the epithelial cells of the sebaceous glands. In rabbits and dogs, directly after such treatment, it may be detected deposited especially in muscle, but it is for the greater part destroyed in the body.<sup>2</sup>

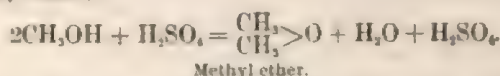
## MONATOMIC ALCOHOL RADICALS.

These are radicals which may be considered as paraffins less one atom of hydrogen, and therefore having one free bond. They form the basis of homologous series of alcohols and acids.

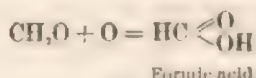
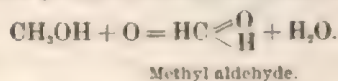
**Monatomic Alcohols** (general formula,  $C_nH_{2n+1}OH$ ).—

Methyl alcohol, $CH_3OH$ .	Amyl alcohol, $C_5H_{11}OH$ .
Ethyl alcohol, $C_2H_5OH$ .	Hexyl alcohol, $C_6H_{13}OH$ .
Propyl alcohol, $C_3H_7OH$ .	Heptyl alcohol, $C_7H_{15}OH$ .
Butyl alcohol, $C_4H_9OH$ .	etc.

**General Reactions for Primary Alcohols.**—(1) Alcohols treated with sulphuric acid give ethers (see Ethyl ether):



(2) Alcohols oxidized give first aldehyde and then acid:

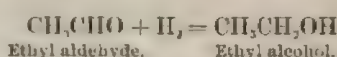


<sup>1</sup> Engler: *Berichte der deutschen chemischen Gesellschaft*, 1888, Bd. 21, S. 1816.

<sup>2</sup> Soubiranski: *Archiv für exper. Pathologie und Pharmacologie*, 1893, Bd. 31, S. 329.

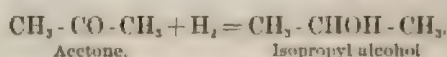


(3) Primary alcohols may be prepared<sup>1</sup> by reduction of the aldehyde with nascent hydrogen,



and similarly by reduction of the acid.

*Secondary Alcohols.*—From propyl alcohol upward there are alcohols isomeric with the primary alcohols, but in which the grouping  $\text{R}-\text{CHOH}-\text{R}$  is characteristic. These are secondary alcohols, and may be produced by the action of nascent hydrogen on ketones:

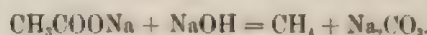


*Tertiary Alcohols.*—These have the general formula  $\text{R}_3-\text{C}\cdot\text{OH}$ .

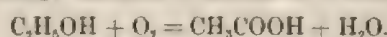
**Monobasic Acids—The Fatty Acids** (formula,  $\text{C}_n\text{H}_{2n}\text{O}_2$ ).—

Formic acid, $\text{H}\cdot\text{COOH}$ .	Capric acid, $\text{C}_9\text{H}_{19}\text{COOH}$ .
Acetic acid, $\text{CH}_3\text{COOH}$ .	Lauric acid, $\text{C}_{11}\text{H}_{23}\text{COOH}$ .
Propionic acid, $\text{C}_2\text{H}_5\text{COOH}$ .	Myristic acid, $\text{C}_{13}\text{H}_{27}\text{COOH}$ .
Butyric acid, $\text{C}_3\text{H}_7\text{COOH}$ .	Palmitic acid, $\text{C}_{15}\text{H}_{31}\text{COOH}$ .
Valerianic acid, $\text{C}_4\text{H}_9\text{COOH}$ .	Stearic acid, $\text{C}_{17}\text{H}_{35}\text{COOH}$ .
Caproic acid, $\text{C}_5\text{H}_{11}\text{COOH}$ .	Arachidic acid, $\text{C}_{19}\text{H}_{39}\text{COOH}$ .
Enanthic acid, $\text{C}_6\text{H}_{13}\text{COOH}$ .	Cerotic acid, $\text{C}_{26}\text{H}_{53}\text{COOH}$ .
Caprylic acid, $\text{C}_7\text{H}_{15}\text{COOH}$ .	Melissic acid, $\text{C}_{29}\text{H}_{59}\text{COOH}$ .

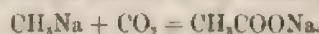
These are organic compounds of acid reaction in which one atom of hydrogen is replaceable by a metal or an organic radical. Combined with glycerin the higher members of the series (from  $\text{C}_4$  up) form the neutral fats of the organism. By distillation of a fatty acid with alkaline hydrate, a hydrocarbon is obtained containing one carbon atom less than the acid used.



*Preparation.*—(a) Through oxidation of alcohols or of aldehydes,

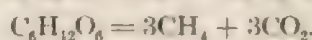
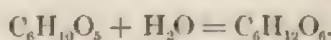


(b) Through the action of carbon dioxide on the sodium compound of alcohol radicals,



#### COMPOUNDS OF METHYL.

**Methane, or Marsh-gas,  $\text{CH}_4$ .**—This gas is produced by intestinal putrefaction, and is the only hydrocarbon found in the body. It is formed in largest quantities from the fermentation of cellulose, which takes place, according to Hoppe-Seyler, thus:

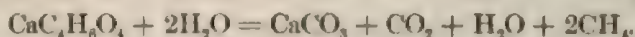


Tappeiner<sup>2</sup> finds that less  $\text{CH}_4$  than  $\text{CO}_2$  is produced in cellulose fermentation in the intestine, and that the lower fatty acids (acetic to valerianic) are also formed. This putrefaction is especially great in the *cæcum* of herbivora. Methane is also a product of putrefaction of proteid (but not of casein, since it is not present when milk is fed). Through the putrefaction of cholin, a

<sup>1</sup> Again attention is called to the fact that the list of these reactions is in no wise complete, but only intended to be suggestive of what should be mastered from a text-book on general chemistry.

<sup>2</sup> *Zeitschrift für Biologie*, 1884, Bd. 20, S. 84.

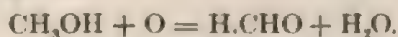
decomposition product of lecithin, methane is likewise evolved in small quantity.<sup>1</sup> Further, methane may be produced from the putrefaction of metallic acetates:



**Properties.**—A colorless, odorless gas which burns with a dull flame. It is absorbed by the blood, and in the herbivora is given off by the lungs often in larger quantity than from the rectum.<sup>2</sup> In man only little is produced. Methane is not oxidized in the body, and is harmless when respired, even when 10 or 20 per cent. in volume is present.<sup>3</sup>

**Trichlormethane, or Chloroform, CHCl<sub>3</sub>.**—This temporarily paralyzes nerves and nerve centres. It is principally removed as vapor through the lungs, but is partially burned, thereby increasing the inorganic chlorides in the urine.<sup>4</sup> After giving chloroform it may itself occur in the urine, and likewise a substance which reduces Fehling's solution, glycuronic acid (which see).

**Methyl Aldehyde, or Formic Aldehyde, H.CHO.**—This may be produced synthetically by passing vapor of methyl alcohol mixed with air over an ignited platinum spiral,



On cooling the vapor, the aldehyde is found dissolved in the alcohol. On evaporation of the alcohol, the aldehyde, through condensation of three of its molecules, forms a crystalline body having the composition (HCHO)<sub>3</sub> and called paraformic aldehyde. This latter treated with calcium or magnesium hydrate again suffers condensation with the production of *formose*, C<sub>6</sub>H<sub>12</sub>O<sub>6</sub>, a sweet-tasting sugar (Butlerow, Loew) identical with *i*-fructose (Fischer). Baeyer<sup>5</sup> first suggested that the sugar synthesis in the plant was analogous to the above process. He conceived the reduction of carbon dioxide to carbon monoxide, which united with chlorophyll, and afterward through hydrogen addition became formic aldehyde; then in upward stages became metaformic aldehyde, sugar, starch, and cellulose. Reinke<sup>6</sup> has shown the presence of formic aldehyde in chlorophyll leaves, and believes its production due to the reduction of carbonic acid through the power of the sun on the leaf, thus:



Bach<sup>7</sup> states that carbonic acid and water in the presence of uranium acetate yield formic aldehyde and nascent oxygen when placed in the sun. According to Stocklase,<sup>8</sup> 400 grams of fresh leaves (128 grams dry) of the sugar beet

<sup>1</sup> Husebroek: *Zeitschrift für physiologische Chemie*, 1888, Bd. 12, S. 148.

<sup>2</sup> B. Tacke: Quoted by Bunge, *Physiologische Chemie*, 3d ed., 1894, S. 284.

<sup>3</sup> Paul Bert: *Comptes rendus de la Société de Biologie*, 1885, p. 523. Abstract in *Malay's Jahresbericht über Thierchemie*, 1886, Bd. 16, S. 364.

<sup>4</sup> A. Zeller: *Zeitschrift für physiologische Chemie*, 1893, Bd. 8, S. 74.

<sup>5</sup> *Berichte der deutschen chemischen Gesellschaft*, 1870, Bd. 3, S. 67.

<sup>6</sup> *Ibid.*, 1881, Bd. 14, S. 2144.

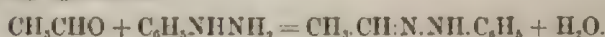
<sup>7</sup> *Ibid.*, 1894, Bd. 28, S. 502 and 689.

<sup>8</sup> Stocklase: *Zeitschrift für physiologische Chemie*, 1895, Bd. 21, S. 83.

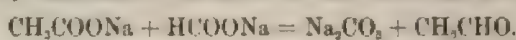


form synthetically and send to the beet root 31 grams of cane-sugar in thirty days.

*General Behavior of Aldehydes.*—They act as reducing agents, being readily oxidized to the corresponding acid. With nascent hydrogen they are reduced to alcohols. A distinctive reaction of aldehydes and ketones is their union with phenyl hydrazin,  $C_6H_5-NH-NH_2$ , giving *hydrazones*:



*Preparation.*—By distillation of the salt of an acid with a salt of formic acid:



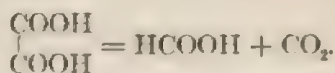
Aceto-aldehyde.

**Methyl Mercaptan,  $CH_3SH$ .**—This is a product of bacterial action on proteid,<sup>1</sup> and is found with  $H_2S$  in the intestine. It is, furthermore, given off on fusing proteid with potash.<sup>2</sup> Methyl mercaptan boils at  $5^\circ$ , and has a strong odor. It is found in the urine, especially after eating asparagus, giving to it a peculiar smell.<sup>3</sup> According to Rubner<sup>4</sup> the smell of cooked cabbage, cauliflower, and the like, is due to methyl mercaptan.

**Methyl Telluride,  $(CH_3)_2Te$ .**—A gas of penetrating odor found in all excreta of an animal after feeding salts of telluric,  $H_2TeO_4$ , or tellurious,  $H_2TeO_3$ , acid. The salt is reduced to metallic tellurium in the body, which unites with a methyl group in some way liberated in the cells.<sup>5</sup> Metallic tellurium may be microscopically seen deposited in various cells, and the odor of  $(CH_3)_2Te$  may be detected for months after the last dose has been given to a dog.<sup>6</sup>

**Methyl Selenide,  $(CH_3)_2Se$ .**—This is very similar to the last-named substance, but more poisonous.

**Formic Acid,  $HCOOH$ .**—Found in ants, and obtained by distilling them with water. Present likewise in stinging-nettles and in the sting of honey-bees, wasps, and hornets, although not the essential poison.<sup>7</sup> Its salts are found in minute quantities in normal urine, and are present especially in both blood and urine in such diseases as leucocythemia, fever, diabetes.<sup>8</sup> Formic acid may be obtained from the oxidation of methyl alcohol, of sugar, and of starch, but not from the latter two in the body. Likewise by heating oxalic acid,



It is found in the urine after feeding methyl alcohol and other methyl derivatives, such as oxymethyl-sulfonic acid, or formic aldehyde. Ethyl alcohol, on the contrary, does not yield it.<sup>9</sup> It is the lowest member of the fatty-acid series, the most volatile, and the least readily oxidized in the body. If formates be

<sup>1</sup> M. Nencki: *Archiv für exper. Pathologie und Pharmacologie*, 1891, Bd. 28, S. 206.

<sup>2</sup> M. Rubner: *Archiv für Hygiene*, 1893.

<sup>3</sup> Nencki, *loc. cit.*

<sup>4</sup> *Loc. cit.*

<sup>5</sup> Hofmeister: *Archiv für exper. Pathologie und Pharmacologie*, 1894, Bd. 33, S. 198.

<sup>6</sup> Beyer: *Archiv für Physiologie*, Jahrgang 1895, S. 225.

<sup>7</sup> Langer: *Archiv für exper. Pathologie und Pharmacologie*, 1897, Bd. 38, S. 381.

<sup>8</sup> See R. Jaksch: *Zeitschrift für physiologische Chemie*, 1886, Bd. 10, S. 537.

<sup>9</sup> Pohl: *Archiv für exper. Pathologie und Pharmacologie*, 1893, Bd. 31, S. 298.

fed they appear readily in the urine. It has a penetrating odor, acts as a reducing agent ( $\text{HCOOH} + \text{O} = \text{CO}_2 + \text{H}_2\text{O}$ ), and therefore precipitates Fehling's solution. Outside of the body it readily undergoes oxidation to water and carbonic acid. It produces inflammation of the skin. A 7 per cent. solution given to a rabbit *per os* has a most powerful corrosive action and results fatally, formic acid being found in the urine.

### ETHYL COMPOUNDS.

**Ethyl Hydroxide, or Ethyl Alcohol,  $\text{C}_2\text{H}_5\text{OH}$ .**—This has been detected in minute quantity in the normal muscle of rabbits, horses, and cattle.<sup>1</sup> Yeast-cells produce a ferment, zymase, which acts to split dextrose into alcohol and carbonic acid, producing likewise, to a very small extent, the higher alcohols, propyl, isobutyl, amyl, the esters of the fatty acids (fusel oil), glycerin, and succinic acid. Such fermentation may to a small extent take place in the intestine,<sup>2</sup> and likewise in the bladder (occurrence in diabetic urine). Pure alcohol is a colorless, almost odorless liquid, having a burning taste. It is a valuable solvent of resins, fats, volatile oils, bromine, iodine, and many medicaments.

*Tinctures* are alcoholic solutions of various drugs and salts.

*Liqueurs* are manufactured from alcohol properly diluted, and treated with sugar and characteristic ethereal oils and aromatics.

*Distilled liquors* are obtained by the distillation of the fermentative products of various substances, whiskey from corn and rye, rum from molasses, brandy from wine. The characterizing taste depends on the different ethereal and fusel oils.

*Wines* are produced from the natural fermentation of grape-juice. Sherry, madeira, and port are fortified by the further addition of alcohol and sugar.

*Beer* is made by converting the starch of barley into maltose and dextrin through diastase. To an aqueous solution of the above hops are added, and the whole is boiled. After the settling of precipitated proteid, etc., the clear supernatant fluid is drawn off and treated with yeast, with ultimate conversion into beer. The taste is furnished by the hops.

**ALCOHOL IN THE BODY.**—Alcohol in the stomach at first prevents the gelatinization necessary in proteid for peptic digestion, but this difficulty is of no great moment because the absorption of alcohol is rapid and complete. It makes the mucous membrane hyperemic, promotes the absorption of accompanying substances (sugar, peptone, potassium iodide), and stimulates the flow of the gastric juice.<sup>3</sup> In this matter it acts as do other condiments (salt, pepper, mustard, peppermint),<sup>4</sup> but if there be too great an irritation on the mucous membrane there is less activity (dyspepsia). The rapid absorption gives to alcohol its quick recuperative effect after collapse, and its value in administering drugs, especially antidotes. Alcoholic beverages combining alcohol and flavor promote gastric digestion and absorption, but often stimulate the appetite in excess of normal requirement. Alcohol is

<sup>1</sup> Rajewski: *Pflüger's Archiv*, 1875, Bd. 11, S. 122.

<sup>2</sup> Macfadyen, Nencki, and Sieber: *Archiv für exper. Pathologie und Pharmacologie*, 1891, Bd. 28, S. 347.

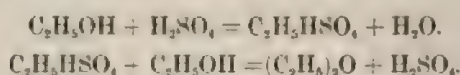
<sup>3</sup> Brandl: *Zeitschrift für Biologie*, 1892, Bd. 29, S. 277. Chittenden, Mendel, and Jackson: *American Journal of Physiology*, 1898, vol. i, p. 164.

<sup>4</sup> Brandl, *Op. cit.*, S. 292.



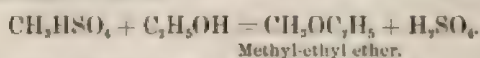
burned in the body, but may also be found in the breath, perspiration, urine, and milk. Alcohol has no effect on proteid decomposition, but acts to spare fat from combustion.<sup>1</sup> The addition of 50 to 80 grams of alcohol to the food has no apparent effect on the nitrogenous equilibrium.<sup>2</sup> Alcohol in the body acts as a paralyzant on certain portions of the brain, destroying the more delicate degrees of attention, judgment, and reflective thought, diminishing the sense of weariness (use after great exertion—furnished to armies in the last hours of battle) and raising the self-esteem; it paralyzes the vaso-constrictor nerves, producing turgescence of the skin with accompanying feeling of warmth and thereby indirectly aiding the heart.<sup>3</sup> Alcohol acts to stimulate the respiration especially in the tired and weak, wine with a rich bouquet like sherry being more effective than plain alcohol.<sup>4</sup> The higher alcohols, propyl, butyl, amyl (see p. 539), are more poisonous as the series ascends,<sup>5</sup> and are less volatile, less easily burned, and therefore more tenaciously retained by the body, with more pernicious results.

**Ethyl Ether,  $C_2H_5O.C_2H_5$ .**—This is formed by the action of sulphuric acid on alcohol, thus:



Ether is a solvent for fats, resins, and ethereal oils. Respired with air its action is like that of chloroform, producing temporary paralysis of the nerves and nervous centres. Since it boils at  $35.5^\circ$  its tension in the blood is always high, and it is probably not burned in the body to any great extent, but when present is eliminated through the breath.

*Ethers* in general are neutral and very stable bodies, and may be considered oxides of organic radicles. They may all be prepared by boiling the corresponding alcohol with sulphuric acid. *Mixed ethers*, in which the radicles are different, are prepared by boiling two different alcohols with sulphuric acid:



**Chloral Hydrate,  $CCl_3CHO + H_2O$  or  $CCl_3CH(OH)_2$ .**—This is the hydrated form of trichlor-ethyl aldehyde,  $CCl_3CHO$ , and is used as an anæsthetic. It is an interesting fact that when fed it partially reappears in the urine as *urochloralic acid*, which consists of trichlor-ethyl alcohol,  $CCl_3CH_2OH$ , combined with glycuronic acid (which see). This is a notable illustration of *reduction* in the body, the change from an aldehyde to an alcohol.

**Acetic Acid,  $CH_3COOH$ .**—Acetic acid, the second of the fatty-acid series, is found in the intestinal tract and in the feces, being a product of putrefaction (see p. 545). It is more easily burned than formic acid, and when absorbed is resolved into  $CO_2$  and water. It is found in traces in the urine, the total amount of fatty acids normally present being 0.008 gram per day.<sup>6</sup> Like formic acid, and accompanied further by the higher acids of the series, it is present in the blood, sweat, and urine in leucocythæmia and diabetes. The

<sup>1</sup> See Rosemann: *Pflüger's Archiv*, 1899, Bd. 77, S. 405.

<sup>2</sup> Ström: Abstract in *Centralblatt für Physiologie*, 1894, Bd. 8, S. 582.

<sup>3</sup> Schmiedeberg: *Grundriss der Arzneimittellehre*, 2d ed., 1888.

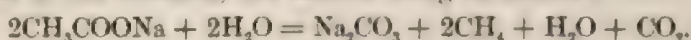
<sup>4</sup> Wendelstadt: *Pflüger's Archiv*, 1899, Bd. 76, S. 226.

<sup>5</sup> Gibbs and Reichert: *Archiv für Physiologie*, 1893, Suppl. Bd. S. 201.

<sup>6</sup> V. Jaksch: *Zeitschrift für physiologische Chemie*, 1886, Bd. 10, S. 536.

probability that acetone is derived from fat renders it possible that these acids may also be derived from fat, and not from abnormal proteid decomposition, as was formerly supposed.

Acetic acid is the product of the oxidation of alcohol. This may be brought about through the presence of spongy platinum, or through the action of bacteria (*Mycoderma aceti*) on dilute alcohol (preparation of vinegar, souring of wine: for reaction see p. 532). Acetic acid, as well as other higher fatty acids, is one of the products derived from proteid through its putrefaction, its dry distillation, its fusion with potash, and its digestion with baryta water in sealed tubes. Formic, acetic, and propionic acids are products of dry distillation of sugar (formation of caramel). These facts are of importance in their relation to the question of the production of fat in the body. Acetic and the higher fatty acids are, further, products of the dry distillation of wood and of the fermentation of cellulose (see p. 532). Putrefaction of acetates may take place in the intestines, the reaction being as follows:



These products are similar to those in the marsh-gas fermentation of cellulose. Vinegar, whose acidity is due to acetic acid, is used as a condiment.

**Acetyl-acetic Acid, or Aceto-acetic Acid,  $\text{CH}_3\text{CO}\cdot\text{CH}_2\cdot\text{COOH}$ .**—This may be considered as acetic acid in which one H atom is replaced by acetyl,  $\text{CH}_3\text{CO}$ —; or as  $\beta$ -keto-butyric acid. Treated with hydrogen it is reduced to  $\beta$ -oxybutyric acid ( $\text{CH}_3\text{CHOH}\cdot\text{CH}_2\cdot\text{COOH}$ ), which in turn may be oxidized to the original substance. Aceto-acetic acid readily breaks up into acetone and carbonic acid:



Aceto-acetic acid, acetone, and  $\beta$ -oxybutyric acid are found in the urine sometimes singly, sometimes together, and probably as the result of a metabolism of fat. In starvation and in diabetes there is an increased excretion of these bodies, for there is an increased metabolism of fat. Feeding fat increases the *acetonuria*, whereas feeding sugar, which protects the fat from destruction, decreases it.<sup>1</sup> From their chemical relations already mentioned these substances may be regarded as of common origin, and in confirmation of this Araki<sup>2</sup> has shown that on feeding  $\beta$ -oxybutyric acid it is oxidized and aceto-acetic acid and acetone may be detected in the urine. The production of the two acids seems to further a gradual neutralization of the blood, ultimately causing coma.<sup>3</sup> In the presence of these substances ammonia runs high in the urine, and in amounts proportional to their excretion<sup>4</sup> (compare p. 550).

Aceto-acetic acid gives to urine in the absence of phosphates a red coloration with ferric chloride (principle of the reaction of Gerhard).

**Amido-acetic Acid, or Glycocoll,  $\text{CH}_2\cdot\text{NH}_2\cdot\text{COOH}$ .**—This is a substance obtained by boiling gelatin with acids or alkalies. It is found in human bile and in that of other animals combined with cholic acid and called glycocholic acid. Chittenden<sup>5</sup> has found glycocoll in the muscles of *Pecten irradians*. It is found in the urine combined with benzoic acid as hippuric acid after

<sup>1</sup> Literature by Waldvogel: *Zeitschrift für klinische Medizin*, 1899, Bd. 38, S. 506.

<sup>2</sup> *Zeitschrift für physiologische Chemie*, 1893, Bd. 18, S. 6.

<sup>3</sup> Münzer and Straaser: *Archiv für exper. Pathologie und Pharmacologie*, 1893, Bd. 32, S. 372.

<sup>4</sup> *Loc. cit.*

<sup>5</sup> *Annalen der Chemie und Pharmakologie*, 1875, Bd. 178, S. 266.



feeding benzoic acid or compounds which the body converts into benzoic acid. In a similar manner phenaceturic acid is found in the urine from the grouping together of glycocholl and phenyl acetic acid. Glycocholl and urea are to be obtained by the decomposition of uric acid through hydriodic acid. Glycocholl forms colorless crystals, soluble in water and having a sweet taste.

*Glycocholl in the Body.*—If glycocholl be fed it is absorbed, burned, and appears as urea in the urine. The fact that dogs, whose bile never contains glycocholic acid, nevertheless excrete hippuric acid after being fed with benzoic acid, indicates that glycocholl may be considered a normal nitrogenous decomposition-product of proteid. Its easy cleavage from gelatin, a product manufactured from proteid in the body, confirms this. Heteroalbumose prepared from fibrin likewise yields glycocholl on decomposition.<sup>1</sup> Continual daily feeding of sufficient benzoic acid to fasting or casein-fed rabbits produces a constant excretion of hippuric acid in such a proportion to total urinary nitrogen as to indicate that 3 to 4 per cent. of the proteid molecule may be split off in metabolism as glycocholl.<sup>2</sup> Feeding gelatin will not increase the hippuric acid excretion as compared with the total urinary nitrogen. So glycocholl may be a cleavage product of both gelatin and proteid metabolism.

*Amido-Acids in General.*—These acids, such as glycocholl, aspartic acid, glutamic acid, leucin, and tyrosin are found as putrefactive products of albumin and gelatin. In these acids the amido-group is very stable, and cannot be removed by boiling with KOH. They are all converted in the body into the amide of carbonic acid (urea). Amido-acids may in general be synthetically formed by heating mono-halogen compounds of the fatty acids with ammonia:



**Methyl Amido-acetic Acid, or Sarcosin,**  $\text{CH}_3\text{NH}_2\text{CH}_2\text{COOH}$ .—This is not found in the body, but is derived from creatin, theobromin, and caffenin by heating with barium hydroxide.

#### PROPYL COMPOUNDS.

**Normal or Primary Propyl Alcohol,**  $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$ .—This is one of the higher alcohols formed in the fermentation of sugar, and on oxidation yields propyl aldehyde and propionic acid.

**Propionic Acid,**  $\text{CH}_3\text{CH}_2\text{COOH}$ .—Combined with glycerin this forms the simplest fat; salts of this acid feel fatty to the touch. Propionic acid is a product of the dry distillation of sugar, of the butyric-acid fermentation of milk-sugar, and of the putrefaction of proteid. It is said to be present in the sweat, in the bile, and sometimes in the contents of the stomach. Like others of the lower fatty acids, it may partially escape oxidation and appear in traces in the urine (see p. 536).

**$\beta$ -Acetyl Propionic Acid, or Levulic Acid,**  $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COOH}$ .—This is the next higher homologue to aceto-acetic acid. It has been obtained only by boiling sugars, especially levulose, with acid and alkalis, and since Kossel and Neumann<sup>3</sup> found that it is yielded by some nucleins they conclude that this indicates the presence of the carbohydrate radical in these nucleins.

<sup>1</sup> Spiro: *Zeitschrift für physiologische Chemie*, 1899, Bd. 28, S. 174.

<sup>2</sup> Parker and Lusk: *American Journal of Physiology*, 1900, vol. iii. p. 472.

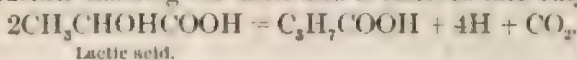
<sup>3</sup> Verhandlung der Berliner physiologischen Gesellschaft, *Archiv für Physiologie*, 1894, S. 536.

**Dimethyl Ketone, or Acetone,  $\text{CH}_3\text{COCH}_3$ .**—This is found normally in the blood and urine, and in especially large quantities in patients suffering from an abnormally large decomposition of fat (see p. 537). During the first day of starvation by Cetti, the starvation artist, the amount of acetone in the urine rose to forty-eight times that of the day previous.<sup>1</sup> It may likewise appear in the breath, giving a characteristic odor. Acetone is a product of the dry distillation of tartaric and citric acids, of wood, and of sugar. Oxidized, acetone yields acetic and formic acids, whereas, treated with hydrogen, it is resolved into secondary propyl alcohol. When acetone is in the urine it is also found in the intestinal canal and in the feces, probably by passage through the intestinal wall.

#### BUTYL COMPOUNDS.

**Normal Butyric Acid,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$ .**—Butyric acid was first found in butter, combined with glycerin. When free it gives the rancid odor to butter, and likewise contributes to the odor of sweat. It has been detected in the spleen, in the blood, and in the urine, but usually only in traces. As a product of putrefaction of proteid, and especially of carbohydrates, it is found in the intestines and in the stomach when the acidity is insufficient to be bactericidal. It contributes to the unpleasant taste after indigestion, through the return of a small portion of the chyme to the mouth. In cheese it is a product of the putrefaction of casein.

If starch, sugar, or dextrin be treated with water, calcium carbonate, and foul cheese, the carbohydrates are slowly converted into a mass of calcium lactate. On further standing the lactic acid is resolved into butyric acid:



Calcium salts are found to putrefy more readily than others, and the carbonate is added above to neutralize any acids formed in the putrefactive process which might inhibit the action of the spores. This same fermentation takes place in the intestinal tract.

**Iso-butyl Alcohol,  $(\text{CH}_3)_2\text{CHCH}_2\text{OH}$ .**—This is found in fusel oil.

**Iso-butyric Acid,  $(\text{CH}_3)_2\text{CHCOOH}$ .**—This is a product of proteid putrefaction and is found in the feces.

#### PENTYL COMPOUNDS.

**Iso-pentyl Alcohol, or Amyl Alcohol,  $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{OH}$ .**—This is the principal constituent of fusel oil, producing the after-effects of distilled-liquor intoxication. The poisonous dose in the dog per kilogram has been found to be—for ethyl alcohol 5–6 grams, for propyl alcohol 3 grams, for butyl alcohol 1.7 grams, for amyl alcohol 1.5 grams<sup>2</sup> (see p. 535).

**Iso-pantoic or Iso-valerianic Acid,  $(\text{CH}_3)_2\text{CHCH}_2\text{COOH}$ .**—This is found in cheese, in the sweat of the foot, likewise in the urine in small-pox, in typhus, and in acute atrophy of the liver. It is a product of proteid putrefaction, and has a most unpleasant odor.

<sup>1</sup> Fr. Müller: *Berliner klinische Wochenschrift*, 1887, S. 428.

<sup>2</sup> Dujardin-Beaumetz et Audigé: *Comptes rendus*, t. 81, p. 19.



## ALCOHOLS CONTAINING MORE THAN FIVE CARBON ATOMS.

Of these, *cetyl alcohol*,  $C_{16}H_{33}OH$ , is found combined with palmitic acid in spermaceti; *cerotyl alcohol*,  $C_{27}H_{55}(OH)$ , is found as an ester in Chinese wax; and *melicyl alcohol*,  $C_{30}H_{61}OH$ , is combined with palmitic acid in beeswax.

## ACIDS CONTAINING MORE THAN FIVE CARBON ATOMS.

**Caproic Acid**,  $C_6H_{11}COOH$ .—This is formed from the putrefaction of proteid, being found in cheese and in feces; it may likewise be detected in the sweat. United with glycerin it occurs in butter-fat.

**Iso-butyl Amido-acetic Acid, or Leucin**,  $(CH_3)_2:CH.CH_2.CHNH_2.COOH$ .—This substance is a constant product of proteid putrefaction, is therefore found in cheese, and may likewise be obtained by boiling proteid or gelatin with sulphuric acid or with alkali. When fed it is converted into urea. When fed to birds the tissues decompose it with elimination of ammonia, which latter may be converted into uric acid by the liver.<sup>1</sup> It is said to occur in pancreatic juice. According to Kühne it is produced in trypsin proteolysis to the extent of 9.1 per cent. of the proteid used. Since this weakly alkaline medium in pancreatic digestion is especially favorable to bacterial activity, Kühne added antiseptic salicylate of sodium and still found leucin (and tyrosin). The same results are obtained with thymol. It is generally accepted that leucin (and tyrosin) are normal products of tryptic digestion. In certain diseases of the liver leucin (and tyrosin) appear in the urine, which may be interpreted to mean that these substances, normally produced from proteid metabolism in the tissues, are not normally burned but accumulate within the body, and are excreted (see below). Proteid on chemical treatment may yield as much as 50 per cent. of leucin. Since leucin contains six atoms of carbon it has been suggested by Fr. Müller that this substance and other proteid cleavage products containing six carbon atoms may be the mother substances of the sugar produced in diabetes. Cohn<sup>2</sup> asserts that feeding leucin to rabbits will increase the glycogen in their livers, but this increase is very slight. But Halsey<sup>3</sup> shows that there is no increase in sugar in the urine after feeding leucin in diabetes. It may be that a sugar radicle in proteid may be the mother-substance of leucin (see p. 581).

Leucin and tyrosin are found in yellow atrophy of the liver both in the urine and in the liver itself, under conditions indicating their production by bacteria and their non-combustion after production. In phosphorus-poisoning and acute anaemia leucin and tyrosin occur in the urine, but apparently without good ground for considering them of bacterial origin.

Leucin crystallizes in characteristic ball-shaped crystals. It was formerly supposed to be amido-caproic acid, but Schulze<sup>4</sup> has shown its true composition. Inactive leucin consists of a mixture of *d*- and *l*-leucin, and may be obtained by treating conglutin with

<sup>1</sup> Minkowski: *Archiv für exper. Pathologie und Pharmacologie*, 1886, Bd. 21, S. 85.

<sup>2</sup> *Zeitschrift für physiologische Chemie*, 1899, Bd. 28, S. 211.

<sup>3</sup> *Sitzungsberichte der Gesellschaft zur Beförderung der gesammten Naturwissenschaften zu Marburg*, 1899, S. 102.

<sup>4</sup> *Berichte der deutschen chemischen Gesellschaft*, 1891, Bd. 24, S. 669; also, Gmelin: *Zeitschrift für physiologische Chemie*, 1893, Bd. 18, S. 38.

$\text{Ba(OH)}_2$ . The two leucins may be separated by fermentation of *d*-leucin with *Penicillium glaucum*. Cleavage of proteid by acids and by putrefaction seems to yield *d*-leucin.<sup>1</sup> Cohn<sup>2</sup> states that several varieties of leucin arise in tryptic digestion.

**Caprylic,  $\text{C}_8\text{H}_{16}\text{O}_2$ , and Capric,  $\text{C}_{10}\text{H}_{20}\text{O}_2$ , Acids.**—These are found as glycerin esters in milk-fat. They are likewise present in sweat and in cheese.

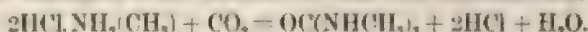
**Palmitic,  $\text{C}_{16}\text{H}_{32}\text{O}_2$ , and Stearic,  $\text{C}_{18}\text{H}_{36}\text{O}_2$ , Acids.**—As glycerin esters these two acids are found in the ordinary fat of adipose tissue, and in the fat of milk. The acids may occur in the feces, and are found combined with calcium in adipocere (p. 560). Wool-fat consists of the cholesterin esters of these acids.

The bile contains palmitic, stearic, and oleic acids,<sup>3</sup> and to these have been attributed its very slight acid reaction.<sup>4</sup>

#### COMPOUNDS OF THE ALCOHOL RADICALS WITH NITROGEN.

**Amines.**—These are bodies in which either one, two, or three of the hydrogen atoms in ammonia are replaced by an alcohol radical, and are termed respectively primary, secondary, and tertiary amines. Methyl, ethyl, and propyl amine bases are the products of proteid putrefaction. They resemble ammonia in their basic properties.

**Methylamine,  $\text{NH}_2(\text{CH}_3)$ .**—This is found in herring-brine. It has the fishy smell noted in decaying fish. It is a product of the distillation of wood and of animal matter. Feeding methylamine hydrochloride is said to cause the appearance of methylated urea in a rabbit's urine<sup>5</sup> (analogous to the formation of urea from ammonia salts):



According to Schiffer,<sup>6</sup> the body, probably through intestinal putrefaction, has the power of partially converting creatin into oxalic acid, ammonia, carbonic acid, and methylamine, which last is finally excreted as methylated urea in the urine.

**Ethylamine,  $\text{C}_2\text{H}_5\text{NH}_2$ ,** when fed as carbonate appears in part as ethylated urea in the urine.<sup>7</sup>

**Trimethylamine,  $\text{N}(\text{CH}_3)_3$ .**—Like ethylamine, this is found in herring-brine and among the products of proteid putrefaction and distillation. In the putrefaction of meat the first ptomaine appearing is cholin, which certainly is derived from lecithin; the cholin (see p. 543) gradually disappears, and in its place trimethylamine may be detected.<sup>8</sup>

#### COMPOUNDS WITH CYANOGEN.

The radicle  $\text{NC—}$  forms a series of bodies not unlike the halogen compounds. Owing to the mobility of the cyanogen group, Pflüger<sup>9</sup> has sought to attribute the properties of living proteid to its presence in the molecule, whereas in the dead proteid of the blood-plasma, for example, he imagines that the nitrogen is contained in an amido- group. When the cyanogen radical occurs in a compound in the form of  $\text{N—C—}$  the body is called a nitril, when in the form of  $\text{C—N—}$  an iso-nitril.

**Cyanogen Gas,  $\text{NC—CN}$ .**—A very poisonous gas.

<sup>1</sup> Gmelin: *Zeitschrift für physiologische Chemie*, 1893, Bd. 18, S. 28.

<sup>2</sup> *Ibid.*, 1895, Bd. 20, S. 203.

<sup>3</sup> Laassar-Cohn: *Ibid.*, 1894, Bd. 19, S. 571.

<sup>4</sup> Jolles: *Pflüger's Archiv*, 1894, Bd. 57, S. 13.

<sup>5</sup> Schiffer: *Zeitschrift für physiologische Chemie*, 1880, Bd. 4, S. 245.

<sup>6</sup> *Loc. cit.*

<sup>7</sup> Schmiedeberg: *Archiv für exper. Pathologie und Pharmacologie*, 1877, Bd. 8, S. 5.

<sup>8</sup> Brieger: Abstract in *Jahresbericht über Thierchemie*, 1885, S. 101.

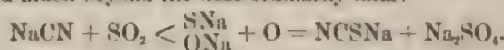
<sup>9</sup> *Pflüger's Archiv*, 1875, Bd. 10, S. 251.



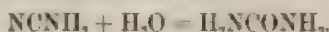
**Hydrocyanic Acid, HCN.**—This is likewise a strong poison. Amygdalin is a glucoside occurring in cherry-pits, in bitter almonds, etc., together with a ferment called emulsin, which latter has the power of transforming amygdalin into dextrose, benzaldehyde, and hydrocyanic acid. Hydrocyanic acid, therefore, gives its taste to oil of bitter almonds, and it may likewise be detected in cherry brandy.

**Potassium Cyanide, KCN.**—This and all other soluble cyanides are fatal poisons.

**Acetonitril, or Methyl Cyanide, CH<sub>3</sub>CN.**—This and its higher homologous nitrils are violent poisons. After feeding acetonitril in small doses, formic acid (see p. 534) and thiocyanic acid (see below) appear in the urine, the thiocyanic acid being a synthetic product of the ingested cyanogen radical, and the HS— group of decomposing proteid.<sup>1</sup> After feeding higher homologues of acetonitril or hydrocyanic acid, thiocyanide likewise appears in the urine. Since the amount of thiocyanide in the urine is normally very small, there is no reason for believing that cyanogen radicals similar to those described above are ever, to any great extent, cleavage-products of proteid.<sup>2</sup> Through intravenous injections of sodium sulphide, and especially of sodium thiosulphate, poisonous cyanogen compounds may be administered much beyond the dose ordinarily fatal.<sup>3</sup>

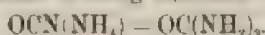


**Cyanamide, NC.NH<sub>2</sub>.**—This is a laboratory decomposition-product of creatin, but does not occur in the body. It is poisonous when administered. When boiled with dilute sulphuric or nitric acids it is converted into urea:



It is to be remembered that creatin in the body is not converted into urea.

**Ammonium Cyanate, OCN(NH<sub>4</sub>).**—Boiling ammonium cyanate converts it into urea. This was shown by Wöhler in 1828, and was the first authoritative laboratory production of a body characteristic of living organisms:



This reaction illustrates Pflüger's idea of the transformation of the unstable cyanogen radical in living proteid into the amido- compound in the dead substance. According to Hoppe-Seyler, the urea-formation in the body is as indicated in the above reaction, but that no cyanic acid or ammonium cyanate is to be detected on account of their extreme instability.

**Potassium Thiocyanide, KSCN.**—This substance is usually found in human saliva to the extent of about 0.01 per cent., and in the urine. Since it contains nitrogen and sulphur its original source must be from proteid. The amount in the urine is probably wholly and quantitatively derived from that in the saliva.<sup>4</sup> If thiocyanides be fed, they appear quickly in the urine without change. Thiocyanides are less poisonous than the simple cyanides (see discussion under Acetonitril above). Thiocyanides give a red color with ferric chloride in acid solution.

#### DIATOMIC ALCOHOL RADICALS.

Thus far only derivatives of monatomic radicals have been discussed; next in order follow diatomic alcohol radicals, represented by the formula C<sub>n</sub>H<sub>2n+1</sub>, and including the bodies *ethylene*, H<sub>2</sub>C = CH<sub>2</sub>, *propylene*, CH<sub>3</sub>—HC = CH<sub>2</sub>, etc. This set of hydrocarbons is called the *olefines*. The first series of compounds which are of physiological interest are the amines of the olefines.

#### AMINES OF THE OLEFINES.

These include the group of *ptomaines*—basic substances which are formed from proteid through bacterial putrefaction. Those which are poisonous are

<sup>1</sup> Lang: *Archiv für exper. Pathologie und Pharmakologie*, 1894, Bd. 34, S. 247.

<sup>2</sup> *Op. cit.*, S. 256.

<sup>3</sup> Lang: *Archiv für exper. Pathologie und Pharmakologie*, 1895, Bd. 36, S. 75.

<sup>4</sup> Gscheidlen: *Pflüger's Archiv*, 1877, Bd. 14, S. 411.

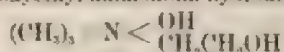
called *toxines*. These bodies are diamines of the olefines, and have been investigated especially by Brieger.<sup>1</sup>

**Tetramethylene-diamin, or Putrescin,**  $H_2N.CH_2.CH_2.CH_2.CH_2.NH_2$ .—This compound is found in putrefying proteid, and has been detected in the urine and feces in cystitis.

**Pentamethylene-diamin, or Cadaverin,**  $H_2N.C_3H_{10}.NH_2$ .—This is found with putrescine wherever produced. They are both found in cultivations of Koch's cholera bacillus and in cholera feces. In cystitis they are a result of special infection of the intestinal tract, are principally excreted in the feces, but are partially absorbed, and prevent, perhaps through chemical union, the burning of cystein normally produced.<sup>2</sup> Diamines are not normally present in the urine.

**Neuridin and Saprin.**—These are isomers of cadaverin and are produced by the same putrefactive processes.

**Cholin.**—This is trimethyl oxyethyl ammonium hydroxide,



and has its source in lecithin decomposition, and putrefaction (see p. 559). Cholin has been found in the cerebrospinal fluid in cases of general paralysis in the insane, and is regarded as the effective poison.<sup>3</sup>

**Muscarin, or Oxycholin.**—This is a violent heart-poison, and may be obtained by treating cholin with nitric acid.

**Neurin.**—This is trimethyl-vinyl ammonium hydroxide,  $(CH_3)_3N < \begin{array}{c} OH \\ | \\ CH = CH_2 \end{array}$ , and is derived from lecithin. It may be considered as derived from cholin, with the elimination of a molecule of water, and it has been shown that bacteria make this conversion. It is a powerful poison. After feeding lecithin and occluding the intestinal canal, cholin and neurin have been found within the intestinal contents.<sup>4</sup>

#### DERIVATIVES OF DIATOMIC ALCOHOLS.

**Taurin, or Amido-ethyl Sulphonic Acid,**  $H_2N.CH_2.CH_2.SO_3H$ .—This has been detected in muscle,<sup>5</sup> in the spleen, and in the suprarenal capsules. It is likewise a usual constituent of the human bile in combination with cholic acid, the salt present being known as sodium taurocholate. Taurin is of proteid origin as is shown by its nitrogen and sulphur content. Little is known regarding its fate in the body, except as is indicated through the behavior of its sulphur atom (see p. 507).

**The Biliary Salts.**—Taurin and glycocholl are found in the bile of cattle in combination with *cholic acid* ( $C_{24}H_{40}O_5$ ). In human bile, according to Lassar-Cohn,<sup>6</sup> there is more *felic acid* ( $C_{23}H_{38}O_4$ ) present than cholic, and there is likewise present some *choleic acid*, ( $C_{24}H_{40}O_4$ ). These acids are of similar chemical structure, though what the structure is, is unknown. Still other acids occur in the bile of pigs, geese, etc. Taurin and glycocholl form compounds with these acids, the sodium salts of which usually make up the major part of

<sup>1</sup> Abstract, *Jahresbericht über Thierchemie*, 1885, S. 101.

<sup>2</sup> Baumann und Udranszky: *Zeitschrift für physiologische Chemie*, 1889, Bd. 13, S. 562, and 1891, Bd. 15, S. 77.

<sup>3</sup> Mott and Halliburton: *Journal of Physiology*, 1899, vol. xxiv. p. ix.

<sup>4</sup> Nesbitt, B.: *American Journal of Physiology*, 1899, vol. ii. p. viii.

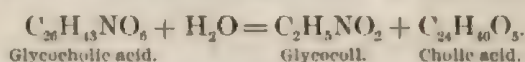
<sup>5</sup> Reed, Kunkenberg, and Wagner: *Zeitschrift für Biologie*, 1886, Bd. 21, S. 30.

<sup>6</sup> *Zeitschrift für physiologische Chemie*, 1894, Bd. 19, S. 570.



the solids of the bile. It has been shown that glycocholl and taurin are found in various parts of the body. Cholic, fellic, etc. acids are only found as products of hepatic activity. In a dog with a biliary fistula the solids of the bile increase on feeding much meat, but the hourly record of the solids compared with the nitrogen in the urine shows that the great production of biliary salts continues after the nitrogen in the urine has begun to decrease.<sup>1</sup> The experiments of Feder<sup>2</sup> have shown that the greater part of the nitrogen in proteid eaten by a dog leaves the body within the first fourteen hours, whereas the excretion of the non-nitrogenous moiety is more evenly distributed over twenty-four hours. It may be fairly concluded that cholic and fellic acids are produced from the non-nitrogenous portion, or from sugar or fat.<sup>3</sup> Furthermore Tappeiner<sup>4</sup> has shown that cholic acid on oxidation yields fatty acids. A synthesis may therefore be effected in the liver between the non-nitrogenous cholic acid formed in the liver from fat or materials convertible into fat, and glycocholl and taurin formed from proteids, whether the latter be produced in the liver or brought to it from the tissues by the blood. That the liver is the place for the synthesis is shown by the fact that the biliary salts do not collect in the body after extirpation of the liver.

The biliary salts in part may be absorbed by the intestine, and a part of these absorbed salts may be again excreted through the bile, forming a circulation of the bile salts. In the intestine either the acid of the gastric juice or bacteria may split up the biliary salt through hydrolysis :



Taurin and glycocholl may be absorbed, while cholic acid is precipitated if in an acid medium, but may be dissolved and absorbed in an alkaline intestine. Hence cholic acid, fellic acid, etc., may often be found in the feces in small amounts. Meconium, that is, the fecal matter of the fetus, contains quantities of the biliary salts, but unaltered, since putrefaction is absent in the fetus. Kühne has described *dyslysin* as a putrefactive product of cholic acid, but its existence is denied by Hoppe-Seyler and Voit. In *icterus* (jaundice), a condition in which the biliary salts return to the blood from the liver, they are burned in the body, sometimes so completely that none appear in the urine. They have the power of dissolving hæmoglobin from the blood-corpuscles, and in consequence the urine may be highly colored, perhaps from bilirubin.<sup>5</sup>

The biliary salts have the power of dissolving the more insoluble fatty acids and soaps produced from the action of steapsin on fats.<sup>6</sup>

Pettenkofer, experimenting once on the conversion of sugar into fat, warmed together cane-sugar, bile, and concentrated sulphuric acid. He obtained no fat, but a strong violet coloration. This is "Pettenkofer's test" for biliary acids (cholic acid, fellic acid, etc.). This coloration is likewise given by proteid, oleic acid, and other bodies. The test of Neu-

<sup>1</sup> Voit : *Zeitschrift für Biologie*, 1891, Bd. 30, S. 545.

<sup>2</sup> *Ibid.*, 1881, Bd. 15, S. 531.

<sup>3</sup> Voit, *Op. cit.*, S. 556.

<sup>4</sup> *Zeitschrift für Biologie*, 1876, Bd. 12, S. 60.

<sup>5</sup> Hoppe-Seyler : *Physiologische Chemie*, 1877, S. 476.

<sup>6</sup> Moore and Rockwood : *Journal of Physiology*, 1897, vol. xxi. p. 58.

komm is a modification of this. Here a drop of a substance containing biliary acids is placed on a small white porcelain cover, with a drop of dilute cane-sugar solution, and one of dilute sulphuric acid: the mixture is then very carefully evaporated over a flame and leaves a brilliant violet stain.

#### OXY-FATTY ACIDS, LACTIC-ACID GROUP.

These are diatomic monobasic acids of the glycols. A glycol is a diatomic alcohol. The oxy-fatty acids have the general formula  $C_nH_{2n}O_3$ , and include:

Carbonic acid,  $CH_2O_3$ .

Oxy-butyric acid,  $C_4H_8O_3$ .

Glycollic acid,  $C_2H_4O_3$ .

Oxy-valerianic acid,  $C_5H_{10}O_3$ .

Lactic acid,  $C_3H_6O_3$ .

etc.

**Carbonic Acid, or Oxy-formic Acid,  $HO.CO.OH$ .**—This is, in reality, a dibasic acid on account of the symmetric structure of the two  $—OH$  radicals. It has already been considered.

**Lactic Acids, or Oxy-propionic Acids.**—Of these there are two isomeres, which vary in the position of their  $—OH$  group, the  $\alpha$ - and  $\beta$ -lactic acids. Physiology is concerned only with the first.

**$\alpha$ -Lactic Acid, or Ethidene Lactic Acid,  $CH_3.CHOH.CO.OH$ .**—This is called *fermentation lactic acid*, being a product of the fermentation of carbohydrates (see p. 539):



On lactic fermentation of milk-sugar depends the souring of milk. This fermentation does not take place in the presence of sufficiently acid gastric juice, but may be more active in the alkaline intestine. It has been noticed that the fecal excrements after a carbohydrate diet react acid, after proteid diet alkaline. The acid reaction is due chiefly if not wholly to acetic acid, since lactic acid, being the stronger acid, is first neutralized by the intestinal alkali. Lactic acid, when absorbed, is completely burned in the body. Lactic-acid fermentation between the teeth dissolves the enamel, and gives bacteria access to the interior. The fermentation lactic acid is inactive to polarized light, and, since it has in its formula an asymmetric carbon atom,<sup>1</sup> it is necessary to assume that it consists of an equal mixture of right and left ethidene lactic acid. On

<sup>1</sup> An asymmetric carbon atom is one in which the four atoms, or groups of atoms, united to

it are all different. In lactic acid we find the following grouping,  $H - \overset{\overset{CH_3}{|}}{C} - OH$ . The central

carbon represents the asymmetric atom. Such an arrangement is always optically active. One is able to conceive the arrangement of the atoms in space, according to the above grouping, or

as follows:  $HO - \overset{\overset{CH_3}{|}}{C} - H$ . This latter represents a different configuration. The two arrange-

ments are optically antagonistic. A mixture of the two is optically inactive. The reader is referred to a text-book on general chemistry for the suggestive illustrations of the tetrahedral space pictures.



standing with *Penicillium glaucum* the left lactic acid is destroyed more freely than is the right, and the solution rotates polarized light to the right.<sup>1</sup>

The right ethidene lactic acid, called also sarco- or para-lactic acid, is that which is found in muscle, blood, in various blood-glands, in the pericardial fluid, and in the aqueous humor. Likewise it is found in the urine after strenuous physical effort, after CO-poisoning, in yellow atrophy of the liver, in phosphorus-poisoning, in trichinosis, and in birds (geese and ducks) after the liver has been extirpated, and it is found in increased quantities in the blood and in all the organs of animals poisoned with arsenic.<sup>2</sup> It is sometimes present in diabetic urine. Para-lactic acid is a normal constituent of the blood and increases in amount after work or tetanus. It accumulates in the dying muscle (*rigor mortis*), causing the formation of  $\text{KH}_2\text{PO}_4$ , which gives the acid reaction and causes coagulation.<sup>3</sup> Some believe that free lactic acid itself is present and aids in the coagulation. Regarding its origin, it has been shown that it increases in amount in the dying muscle without simultaneous decrease in the amount of glycogen.<sup>4</sup> It has also been shown that the large increase of lactic acid in the extirpated liver is only due to the production of fermentation lactic acid from glycogen.<sup>5</sup> On extirpation of the liver in geese,<sup>6</sup> ammonia and para-lactic acid replace the customary uric acid in the excreta, and previous ingestion of carbohydrates or of urea will not increase the amount of para-lactic acid. The lactic acid excreted is proportional in amount to the proteid destroyed and to the ammonia present. It may fairly be concluded that it always owes its origin to proteid.

Hoppe-Seyler<sup>7</sup> says that lactic acid appears in the urine only when there is insufficient oxidation in the body, and attributes its derivation to the decomposition of glycogen. In CO-poisoning Araki<sup>8</sup> finds as much as 2 per cent. of lactic acid (reckoned as zinc lactate) in a rabbit's urine. Minkowski,<sup>9</sup> on the other hand, denies the insufficient-oxidation theory, and maintains that the destruction of lactic acid depends on a specific property of the liver, the normal action being either destruction in the liver itself or in other organs through the medium of a substance (enzyme?) produced in the liver.

One may interpret Araki's experiment as showing that considerable quantities of lactic acid are constantly produced in metabolism, but are normally swept away and burned; the CO-poisoning would prevent the normal combustion. The accumulation in muscle after stoppage of the blood-current (*rigor mortis*) would then be only a continuation of the normal process of decomposition.

**Cystein,  $\alpha$ -Amido- $\alpha$ -thiopropionic Acid.**—This substance has the formula

<sup>1</sup> *Berichte der deutschen chemischen Gesellschaft*, Bd. 16, S. 2720.

<sup>2</sup> Morishima: *Archiv für exper. Pathologie und Pharmacologie*, 1899, Bd. 43, S. 217.

<sup>3</sup> Astaschewski: *Zeitschrift für physiologische Chemie*, 1880, Bd. 4, S. 403; Irisawa, *Ibid.*, 1893, Bd. 17, S. 351.

<sup>4</sup> Boehm: *Pflüger's Archiv*, 1880, Bd. 23, S. 44.

<sup>5</sup> Morishima: *Loc. cit.*

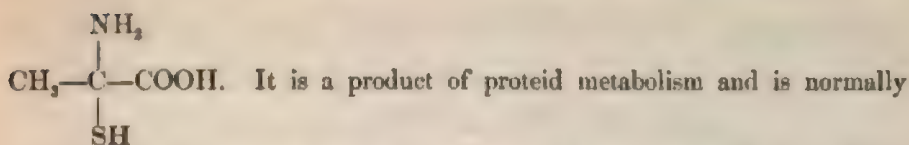
<sup>6</sup> Minkowski: *Archiv für exper. Pathologie und Pharmacologie*, 1886, Bd. 21, S. 41.

<sup>7</sup> *Festschrift zu R. Virchow's 70. Geburtstag*.

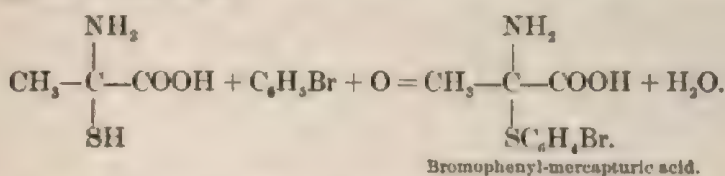
<sup>8</sup> *Zeitschrift für physiologische Chemie*, 1894, Bd. 19, S. 426.

<sup>9</sup> *Loc. cit.*, and *Archiv für exper. Pathologie und Pharmacologie*, 1893, Bd. 31, S. 214.

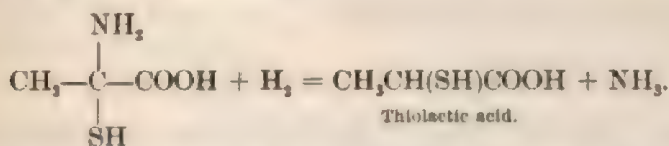
*m. abramo*



destroyed in the body. On the introduction of a halogen derivative of benzol into the body, compounds are formed with cystein, called *mercapturic acids*, which appear in the urine:

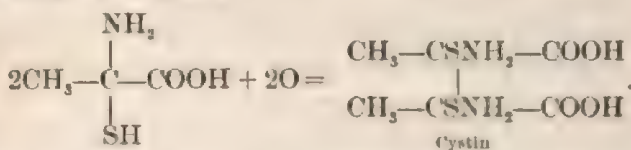


This proves that cystein (like glycocoll, for example) is at least an intermediary and possibly a primary product of proteid metabolism. If cystein be fed, the greater part (two-thirds) of the sulphur appears in the urine as sulphuric acid, the rest as neutral sulphur. *Thiolactic acid* has been found<sup>1</sup> as a decomposition product of horn. Baumann<sup>2</sup> demonstrates the reduction of cystein to thiolactic acid, shows that the latter yields an odor of ethyl sulphide on evaporation, and asks if thiolactic acid be not the mother substance of Abel's compound (see p. 507):



Cystein itself is never directly detected in the urine or in the body.

**Cystin, Dithio-diamido-ethidene Lactic Acid.**—Cystein is converted by atmospheric oxygen into cystin:



Cystin is very insoluble in water. In particular cases it appears in considerable quantities as a urinary sediment, still more rarely as a stone in the bladder (see p. 543). It has been detected in the normal livers of horses.<sup>3</sup> It is *laevo-rotatory*.

It is reported<sup>4</sup> that bodies having the composition C—S—H (thio-acids, mercaptans) may form sulphuric acid, while most of those having the composition —C—S—C— (ethyl sulphide) are not oxidized in the body.

<sup>1</sup> Suter: *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, S. 564.

<sup>2</sup> Baumann: *Ibid.*, 1895, Bd. 20, S. 583.

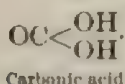
<sup>3</sup> Drechsel: *Zeitschrift für Biologie*, 1897, Bd. 33, S. 85.

<sup>4</sup> W. J. Smith: *Pföger's Archiv*, 1894, Bd. 55, S. 542, and 1894, Bd. 57, S. 418.

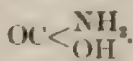


**$\beta$ -Oxybutyric Acid,  $\text{CH}_3\text{CHOHCH}_2\text{COOH}$ .**—A *lævo*-rotatory acid (see p. 539).

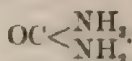
#### AMIDO-DERIVATIVES OF CARBONIC ACID.



Carbonic acid.



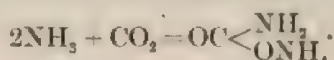
Carbamic acid.



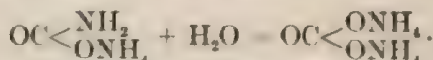
Carbamide.

**Carbamic Acid.**—This is not known free, but its calcium salts have been found, especially in herbivorous urine, and its presence in the blood as ammonium carbamate is maintained.<sup>1</sup> The latter has been obtained by Drechsel<sup>2</sup> by oxidizing glycocoll and leucin in ammoniacal solution, and he has converted it into urea by electrolysis. From these facts he concludes that ammonium carbamate is the antecedent of urea. It must, however, be remembered that ammonium carbamate is very readily decomposable, and has never been directly detected in the blood.

Ammonium carbamate is formed by the direct union of ammonia with carbonic oxide in their nascent states, and is therefore found in commercial ammonium carbonate and as the product of the oxidation of the amido-compounds above mentioned :

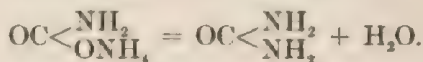
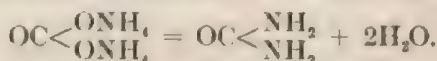


Water converts it into ammonium carbonate :



**Carbamide, or Urea,  $\text{OC}(\text{NH}_2)_2$ .**—This is the principal end-product of the nitrogenous portion of proteid in all mammals, being found in considerable concentration in the urine. Schöndorff<sup>3</sup> finds in the blood, liver, spleen, pancreas, and brain about 0.12 per cent. of urea, while muscle contains 0.09 per cent., the heart 0.17 per cent., and the kidney 0.67 per cent. In uræmia it may collect in all tissues of the body, and may then be excreted in slight amount by the gastric and intestinal juices. It is given off in profuse sweating, though only in small proportion to that lost in the urine.

**Preparation.**—(1) Like other amides, by heating ammonium carbonate ; further, by the electrolysis of, or by heating, ammonium carbamate :

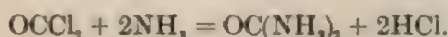


(2) Through the union of ammonia with carbonyl chloride :

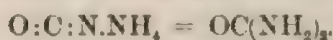
<sup>1</sup> Drechsel : *Ludwig's Arbeiten*, 1875, S. 172 ; Drechsel und Abel, *Archiv für Physiologie*, 1891, S. 242.

<sup>2</sup> *Loc. cit.*

<sup>3</sup> *Pflüger's Archiv*, 1899, Bd. 74, S. 307.



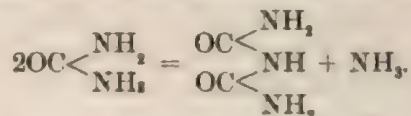
(3) By evaporating an aqueous solution of ammonium cyanate:



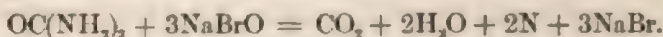
This was Wöhler's notable preparation in 1828 of an "organic" compound, a product of life, without the aid of a "vital force."

(4) From proteid, through hydrolytic cleavage<sup>1</sup> (see p. 551). This origin has not as yet been confirmed.

*Properties.*—Urea is a weak base, of great stability when within the alkaline fluids and tissues of the body. It is soluble in water in all proportions, very soluble in hot, less so in cold alcohol, whence it crystallizes in needle-like forms. It melts at 132° and recrystallizes on cooling. Heated higher it is converted into biuret, a substance which gives a violet color with dilute cupric sulphate in a sodium-hydrate solution (called the biuret reaction):



Heating urea with water over 100° in sealed tubes, boiling it with alkalis or acids, bacterial action (see p. 512), all convert it through hydrolysis into carbonic oxide and ammonia. Such decomposition may take place in the stomach in uræmia.<sup>2</sup> Hypobromite of sodium in the presence of alkali acts to break up urea, thus:



The alkali present absorbs the  $\text{CO}_2$ , and the volumes of N afford a measure for the amount of urea present (method of Hüfner, apparatus by Doremus).

Urea combines with nitric acid to form urea nitrate,  $\text{OC}(\text{NH}_2)_2.\text{HNO}_3$ , which is insoluble in nitric acid. Urea oxalate, which is formed in similar manner by the combination of urea with oxalic acid, is insoluble in water. Many combinations with metallic salts have been prepared, of which one with mercuric nitrate, of uncertain formula, is the basis of Liebig's method of titration for urea.

**UREA IN THE BODY.**—This subject has been discussed under Nutrition. It can be considered here only briefly. When urea is fed it is rapidly excreted in the urine. The excreted nitrogen of proteid appears in mammalia in greater part as urea. Amido-products of proteid decomposition, glycocoll, leucin, aspartic acid, uric acid, when fed are converted by the body into urea. So likewise are ammonium carbonate, lactate, and tartrate. Ammonium chloride, on account of the strong acid radical, passes through carnivora unchanged, but in herbivora, the blood of which is more strongly alkaline, a certain part of the ammonia is converted first into carbonate and then into urea. This conversion of ammonium carbonate into urea is of striking interest. Artificial irrigation of a liver with blood containing ammonium carbonate increases the urea in

<sup>1</sup> Drechsel: *Archiv für Physiologie*, 1891, S. 261.

<sup>2</sup> Voit: *Zeitschrift für Biologie*, 1868, Bd. 4, S. 150.



the blood, while similar treatment of muscle or kidney shows no such results.<sup>1</sup> In other experiments it has been shown that ammonium salts appear in the urine after feeding acids to carnivora, and that in disease in which acids are produced (lactic, aceto-acetic, oxybutyric acids) ammonia accompanying them is found in the urine, in all cases representing that ordinarily converted into urea. In disease of the liver (cirrhosis, phosphorus-poisoning) ammonia is found in the urine above the normal. If the liver be excluded from the dog's circulation by Eck's fistula, ammonium salts accumulate in the blood. If an amido body like glycocoll be fed to such a dog, ammonium salts rapidly accumulate, which indicates the normal fate of glycocoll.<sup>2</sup> Amido acids, such as glycocoll, leucin, etc., which are cleavage products of proteids, and which are known to burn to urea, are nevertheless highly resistant to strong chemical reagents, either alkalies or acids. Lewi's<sup>3</sup> work indicates that a ferment present in the liver (and perhaps elsewhere) may convert these stable compounds into others in which the nitrogen is less firmly combined, which may in turn be converted into urea. Admitting the fact that ammonium carbonate (and carbamate likewise) may be converted into urea by the liver, there is no ground for believing that this is the normal process for the production of the whole amount of urea, nor is there at present any measure of the amount of ammonium-salts produced in the body. The liver may be very completely destroyed by disease, and large quantities of urea still be excreted.<sup>4</sup> In geese extirpation of the liver has no effect on the urea excreted, therefore in geese it is formed elsewhere.<sup>5</sup> For aught that is known, therefore, urea may be formed in other organs than the liver, and it is not at all improbable that it is formed in all organs where proteid decomposition is progressing. The greater part of urea from proteid is eliminated in the dog fourteen hours after his meal (see p. 544).

**Guanidin**,  $\text{HN}:\text{C} < \begin{smallmatrix} \text{NH}_2 \\ \text{NH}_2 \end{smallmatrix}$ . This is the imide of urea, and has been obtained by the oxidation of guanin. It unites with alcohol and acid radicals—forming, for example, methyl guanidin,  $\text{HNC} < \begin{smallmatrix} \text{NH}_2 \\ \text{NHCH}_3 \end{smallmatrix}$ , and guanidin acetic acid,  $\text{HN} < \begin{smallmatrix} \text{NH}_2 \\ \text{NHCH}_2\text{COOH} \end{smallmatrix}$ .

**Creatin, or Methyl Guanidin Acetic Acid**,  $\text{HNC} < \begin{smallmatrix} \text{NH}_2 \\ \text{N}(\text{CH}_3)\text{CH}_2\text{COOH} \end{smallmatrix}$ . Creatin is a product of proteid decomposition and found in muscle to the extent of 0.3 per cent., in traces in the blood, and in varying amounts in the urine. It is the principal constituent of meat-extracts (Liebig's). Creatin may be formed synthetically by the union of cyanamide with sarcosin, and it may be broken up into these constituents by boiling with barium hydrate, but the cyanamide is immediately converted into urea through the addition of water:

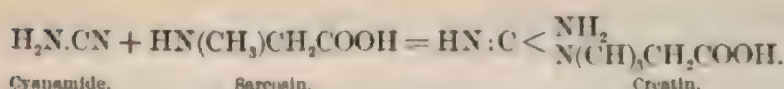
<sup>1</sup> Von Schroeder: *Archiv für exper. Pathologie und Pharmacologie*, 1882, Bd. 15, S. 364.

<sup>2</sup> Salaskin, S.: *Zeitschrift für physiologische Chemie*, 1898, Bd. 25, S. 449.

<sup>3</sup> *Zeitschrift für physiologische Chemie*, 1898, Bd. 25, S. 511.

<sup>4</sup> Marfort: *Archiv für exper. Pathologie und Pharmacologie*, 1894, Bd. 33 S. 71.

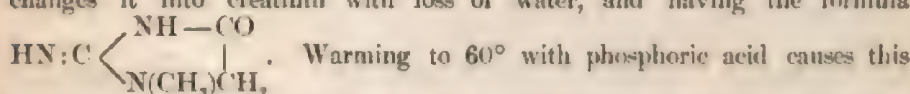
<sup>5</sup> Minowski: *Ibid.*, 1886, Bd. 21, S. 62.



Creatin, however, is not converted into urea in the body if fed, but is excreted in the urine as creatinin.<sup>1</sup> The amount of creatinin found in the urine corresponds normally to the amount of creatin contained in the meat food; in starvation urine it is proportional in amount to the proteid (muscle) destroyed, being present even on the thirtieth day (experiment on Succi<sup>2</sup>); and it is present only in traces, or not at all, in the urine of milk-fed children (creatin-free food). In convalescence creatin is said to be retained, possibly for the building of new muscle.<sup>3</sup> There is no reason for believing that much creatin is ever formed in the body.

Creatin gives its flavor to meat. If gently heated it gives the odor of roasting beef. Creatinin in the urine reduces alkaline solutions of copper salts (care must be taken, therefore, in making the sugar test after using meat extracts). The action of creatin is simply that of a pleasant-tasting, pleasant-smelling substance, which prepares the stomach for food but has no nourishing value *per se*. It is considered by some to be a nerve-stimulant.

**Creatinin, or Glycolyl Methyl Guanidin.**—Heating creatin with acids changes it into creatinin with loss of water, and having the formula



Warming to 60° with phosphoric acid causes this conversion. In like manner when the kidney prepares an acid urine, creatin becomes creatinin: if the acid reaction be effaced through feeding alkaline salts the creatin is excreted unchanged.<sup>4</sup> Creatinin with chloride of zinc forms a characteristic very insoluble white powder of creatinin zinc chloride,  $(\text{C}_4\text{H}_7\text{N}_3\text{O})_2 \cdot \text{ZnCl}_2$ .

**Lysatin,  $\text{C}_6\text{H}_{13}\text{N}_2\text{O}_2$ , and Lysatinin,  $\text{C}_6\text{H}_{11}\text{N}_3\text{O}_2$ .**—These substances are obtained, like lysin (see below), from the hydrolytic cleavage of proteid, as for example from casein or conglutin heated with hydrochloric acid and zinc chloride; they are probably likewise produced in trypsin digestion.<sup>5</sup>

According to Drechsel<sup>6</sup> they are homologues of creatin and creatinin, and therefore should yield urea on heating with barium hydroxide. This is Drechsel's method of direct production of urea from proteid by hydrolytic cleavage.

**Diamido- Fatty Acids.**—Of these four have been described:

**Diamido-acetic Acid,  $\text{CH}(\text{NH}_2)_2\text{COOH}$ .**—This was found by Drechsel<sup>7</sup> among other compounds after heating casein in sealed tubes with concentrated hydrochloric acid at 140°. *Diamido-propionic acid* has not been found in the body.

<sup>1</sup> Voit: *Zeitschrift für Biologie*, 1868, Bd. 4, S. 114.

<sup>2</sup> Luciani: *Das Hungern*, Leipzig, 1890, S. 144.

<sup>3</sup> Von Noorden: *Pathologie des Stoffwechsels*, 1893, S. 169.

<sup>4</sup> Voit: *Zeitschrift für Biologie*, 1868, Bd. 4, S. 150.

<sup>5</sup> See Drechsel, and his pupils Fisher, Siegfried, and Hedin: *Archiv für Phynologie*, 1891, S. 248 *et seq.*

<sup>6</sup> *Op. cit.*, S. 261.

<sup>7</sup> Abstract in Maly's *Jahresbericht über Thierchemie*, 1892, S. 9.



**Diamido-valeric Acid, or Ornithin,**  $C_4H_7(NH_2)_2COOH$ .—This has been detected by Jaffe in the urine and excrements of fowls.

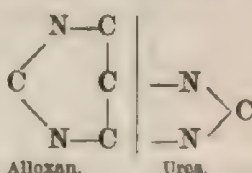
**$\alpha$ - $\epsilon$ -Diamido-caproic Acid, or Lysin,**  $CH_2NH_2CH_2CH_2CH_2CHNH_2COOH$ .—This is a hydrolytic cleavage product of proteid after boiling with hydrochloric acid, or baryta water,<sup>1</sup> and may be similarly obtained from gelatin, from vegetable proteid (conglutin), from the pancreatic digestion of proteid, and from the decomposition of the protamins. Other bases are :

**Histidin,**  $C_6H_7N_3O_2$ , a base derived from all proteids and from protamins.

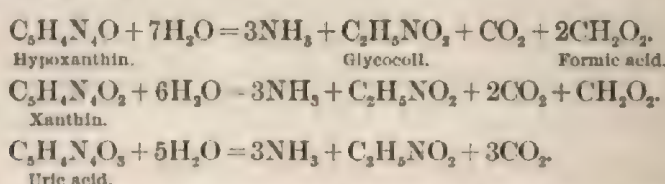
**Arginin,**<sup>2</sup>  $CNH \begin{matrix} \nearrow NH_2 \\ \searrow NH-CH_2-CH_2-CH_2-CHNH_2COOH \end{matrix}$ , is also derived from all proteids and from protamins.

#### PURIN OR ALLOXURIC BODIES AND BASES.

The alloxuric bodies comprise those containing in combination two radicals, one of *alloxan*,  $OC < \begin{matrix} NH-CO \\ NH-CO \end{matrix} > CO$ , the other of urea. The skeletal structure of all alloxuric bodies may be written thus :



These bodies fall into three groups, that of hypoxanthin, of xanthin, and of uric acid. Bodies belonging to the first two groups are called *alloxuric bases*, or more commonly *xanthin bases*, or *nuclein bases*, because they are derived from nuclein. The strong family analogy of the three groups is shown by the following reactions—results of heating with hydrochloric acid in sealed tubes at  $180^\circ$  to  $200^\circ$  :<sup>3</sup>



Reference to the formulæ below will show that the molecules of  $CO_2$  given off correspond to the number of  $CO$  radicals in the alloxuric body, while the molecules of formic acid correspond to the number of  $CH$  groups.

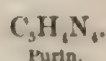
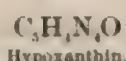
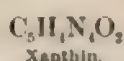
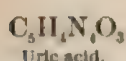
Emil Fisher<sup>4</sup> has discovered a body called purin, and has given another classification. The chemical series of the purin bodies may thus be presented :

<sup>1</sup> Drechsel : *Archiv für Physiologie*, 1891, S. 248.

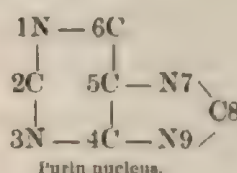
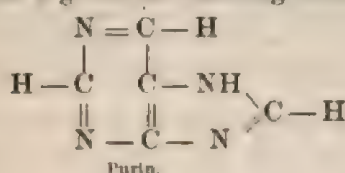
<sup>2</sup> Formula by Schulze and Winterstein : *Zeitschrift für physiologische Chemie*, 1899, Bd. 26, S. 12.

<sup>3</sup> Krüger : *Ibid.*, 1894, Bd., 18, S. 463.

<sup>4</sup> *Berichte der deutschen chemischen Gesellschaft*, 1899, Bd. 32, S. 435.



To purin is given the following formula :



For the convenience of chemical description the atoms of the purin nucleus are numbered as above, since the chemical constitution varies with the locality to which the atoms are attached to the nucleus. The purin derivatives number many hundreds, but only about a dozen are known at present to have physiological significance.

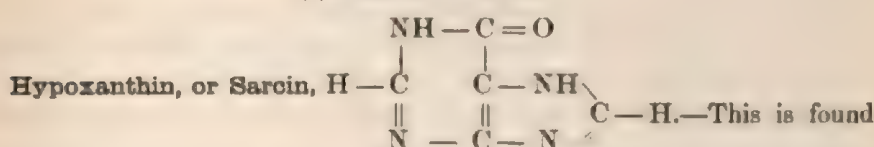
Hypoxanthin is 6-oxypurin, xanthin is 2, 6-dioxypurin, uric acid is 2, 6, 8-trioxypurin, adenin is 6-amino-purin, while guanin is 2-amino-6-oxypurin.

Hypoxanthin, xanthin, adenin, and guanin are decomposition products of the nucleins, and from their oxidation uric acid is derived.

#### (a) PURINS.

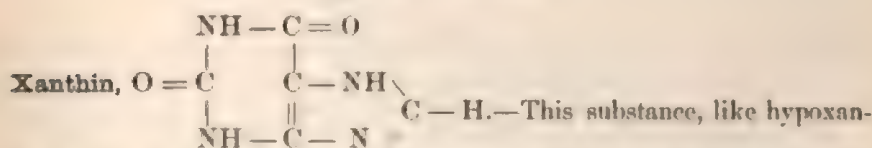
**Purin**,  $\text{C}_5\text{H}_4\text{N}_4$ . This, according to Emil Fisher, is a substance which may occur in the body, but which on account of its ready decomposition has not yet been discovered there.

#### (b) MONOXYPURINS.



in small amount in the tissues and fluids of the body and in the urine. Hypoxanthin is derived from some nucleins, especially those contained in the sperm of salmon and carp, through the action of water or dilute acids.

#### (c) DIOXYPURINS.



thin, is found in the tissues and fluids of the body and in the urine. It is a decomposition product of some nucleins and may be found in those of the pancreas, thymus, testicle, carp sperm, etc.

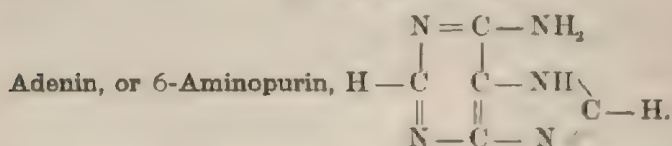
**Methyl Dioxypurins.**—The alkaloids theophyllin, theobromin, and caffen occur in tea, coffee, cocoa, etc., and are habitually taken in the food. Theophyllin (1, 3-dimethyl-



xanthin) probably loses its labile 3-methyl in the body, and occurs in the urine as 1-methyl-xanthin. In like manner theobromin (3, 7-dimethylxanthin) is converted into heteroxanthin (7-methylxanthin). Caffein (1, 3, 7-trimethylxanthin) also parts with its 3-methylradicle and appears in the urine as paraxanthin (1, 7-dimethylxanthin). Krüger and Salomon<sup>1</sup> find 22.3 grams of heteroxanthin, 31.3 grams of 1-methylxanthin, and 15.3 grams of para-xanthin in 10,000 liters of urine, or much more in quantity than the true nuclein bases (xanthin, etc.).

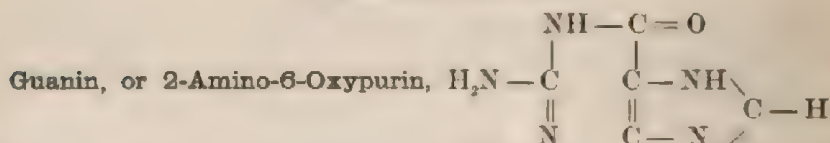
That theophyllin, theobromin, and caffein may be demethylated in the tissue is an interesting commentary on the methylation of tellurium, selenium, and pyridin by the tissues.

(d) MONOAMINOPURINS.



Adenin is found in the blood, the tissues, and the urine. It is especially a decomposition product of thymus nuclein, although other nucleins may contain it. Nitrous oxide converts it into hypoxanthin.

(e) AMINOXYPURINS.



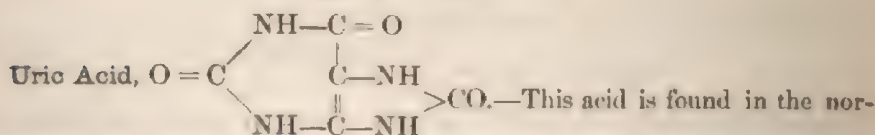
This also is found as a decomposition product of some nucleins, especially that of the pancreas. Combined with calcium it gives the brilliant iridescence to fish-scales.<sup>2</sup> It is found in the fresher layers of guano, and, according to Voit, is here very probably derived from the fish eaten by the water-fowl.

**Epiguanin, or 7-Methyl-guanin.**—This has been found in the urine, and like the other methylated purins may very likely be derived from the food fed.<sup>3</sup>

**Episarcin** is a purin base which has been found in the urine, but whose configuration has not yet been made out.

**Carnin** is said to occur in the urine. Its composition is unknown.

(f) TRIOXYPURINS.



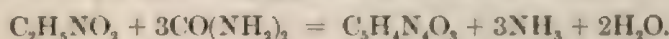
<sup>1</sup> *Zeitschrift für physiologische Chemie*, 1898, Bd. 26, S. 350.

<sup>2</sup> Voit: *Zeitschrift für wissenschaftliche Zoologie*, Bd. 15, S. 515.

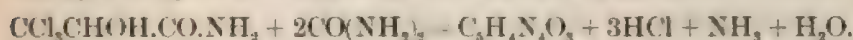
<sup>3</sup> Krüger and Salomon: *Zeitschrift für physiologische Chemie*, 1898, Bd. 26, S. 389.

especially in gout. It is the principal excrement of birds and snakes, that of the latter being almost pure ammonium urate.

*Preparation.*—(1) By heating glycocoll with urea at  $200^{\circ}$ :

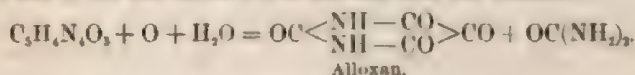


(2) By heating the amide of trichlorolactic acid with urea:

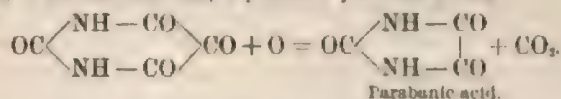


*Properties.*—Uric acid may be deposited in white hard crystals, which are tasteless, odorless, and almost insoluble in water, alcohol, or ether. (For its solution in the urine see p. 522.) Presence of urea adds to its solubility.<sup>1</sup> Its most soluble salts are those of lithium and piperazin. Uric acid is dibasic—that is, two of its hydrogen atoms may be replaced by monad elements.

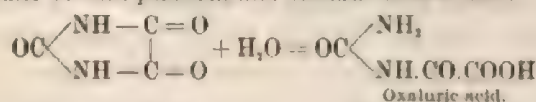
(1) Nitric acid in the cold converts uric acid into urea and *alloxan*:



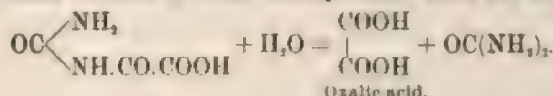
(2) Whereas, if the hot acid acts, it produces *parabanic acid*:



(3) Through water addition parabanic acid becomes *oxaluric acid*:

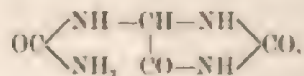


(4) And still another molecule of water added produces oxalic acid and urea:<sup>2</sup>



The above reactions lead up to the constitutional formula of uric acid, and show its decomposition into urea and oxalic acid through oxidation and hydrolysis. It is known that uric acid when fed increases the amount of urea in the urine, and it is possible that the oxalic acid in the urine may have the same source.

Uric acid oxidized with permanganate of potassium is converted into *allantoin*,



a substance which is found in the allantoic fluid, and in the urine of pregnant women and of newborn children, and in the urine of dogs after feeding thymus (see below).

If uric acid be carefully evaporated with nitric acid on a small white porcelain cover, a reddish residue remains, which moistened with ammonia gives a brilliant purple color, due to the formation of *murexid*,  $\text{C}_8\text{H}_4(\text{NH}_2)\text{N}_5\text{O}_4$ ; subsequent addition of alkali gives a red coloration. This is known as the *murexid test* and is very delicate.

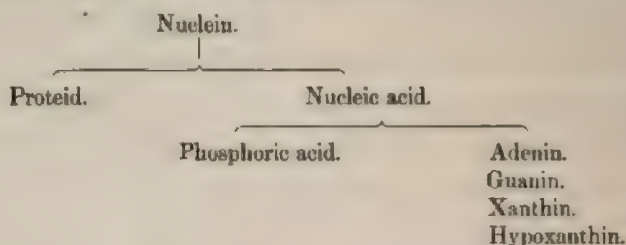
**The Purin Bases in the Body.**—All true nucleins yield one or more of the purin bases. Nucleins are combinations of nucleic acid and proteid,

<sup>1</sup> G. Rüdel: *Archiv für exper. Pathologie und Pharmacologie*, 1893, Bd. 30, S. 409.

<sup>2</sup> See Bunge: *Physiologische Chemie*, 1894, S. 312.



except the nuclein from spermatozoa in which the acid combines with protamin. The simplest indication of the cleavage of nuclein (see Nuclein) on chemical treatment, may be written as follows :



The idea that the purin bodies occurring in the urine of mammals are the metabolic products of nucleins, the uric acid being derived from the oxidation of the bases, was made especially clear by the experiments of Horbaczewski.<sup>1</sup> His statement that feeding nucleins increases the purin bases and the uric acid in the urine has been frequently confirmed. He also showed that if fresh spleen pulp, which contains no purin bodies, be permitted to putrefy, the extract will contain xanthin and hypoxanthin, whereas if the spleen pulp be shaken with the air uric acid is produced, being oxidized from these bases. Spitzer<sup>2</sup> finds, if air be passed through spleen and liver extracts digested at 40° with the exclusion of putrefaction, that uric acid is produced. The nuclein bases formed decrease with the increase of uric acid. Hypoxanthin and xanthin added to such digests are readily oxidized to uric acid, as are adenin and guanin, although with greater difficulty. Extracts of the kidney, pancreas, thymus, and blood have no such power. Feeding uric acid and nuclein bases increases the amount of urea in the urine. Minkowski<sup>3</sup> has proved that after feeding hypoxanthin uric acid increases in the urine, showing its oxidation. Minkowski also showed after feeding a man with thymus, the nuclein of which yields principally adenin with some guanin, that the amount of uric acid was increased in the urine; the same food fed to a dog increased the uric acid, and allantoin, an oxidation product of uric acid, also appeared. Feeding adenin to a dog did not increase the uric acid or allantoin excretion, but on autopsy of the dog there was found a deposit of uric acid in the uriniferous tubules with indications of inflammatory processes. This is the first known artificial production of a deposition of uric acid. It would seem that the adenin in combination with nucleic acid in thymus may be readily burned to uric acid in such a way that it is readily excreted, whereas adenin itself behaves differently. Loewi<sup>4</sup> finds that the same amount of nuclein food fed to different people results in the same excretion of uric acid. He therefore concludes that all the purin bodies liberated in metabolism are quantitatively eliminated. The analysis of

<sup>1</sup> *Sitzungsberichte der Wiener Akademie der Wissenschaft*, 1891, Bd. 100, Abth. iii. S. 13.

<sup>2</sup> *Pflüger's Archiv*, 1899, Bd. 76, S. 192.

<sup>3</sup> *Archiv für exper. Pathologie und Pharmacologie*, 1898, Bd. 41, S. 375.

<sup>4</sup> *Ibid.*, 1900, Bd. 44, S. 1.

10,000 liters of urine<sup>1</sup> has shown the presence of 10.11 grams of xanthin, 8.5 grams of hypoxanthin, and 3.54 grams of adenin.

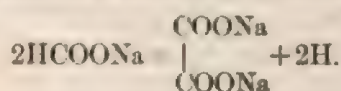
Xanthin fed to birds is converted into uric acid. In birds the formation of uric acid depends on a synthetic union of ammonia and lactic acid in the liver, since on extirpation of the liver the last two substances appear in the urine in amounts proportional to the normally formed uric acid (see p. 546).

The literature on the subject of gout is enormous. It is sufficient to remark here that it is not even known whether gout is due to an increased formation or an increased retention of uric acid. The amount of uric acid in the blood is certainly increased. The normal amount of uric acid in the daily urine is put at 0.7 gram, that of the purin bases at 0.1325,<sup>2</sup> although this latter may be too high on account of the presence of the bases derived from tea and coffee. The amount of the bases may be quadrupled in leucocythæmia.<sup>3</sup>

#### DIATOMIC DIBASIC ACIDS, $C_nH_{2n-2}O_4$ .

**Oxalic Acid,**  $\begin{array}{c} \text{COOH} \\ | \\ \text{COOH} \end{array}$ .—This is found as calcium oxalate in the urine, and

is present in most plants. It is a product of boiling proteid with barium hydrate. It may be obtained synthetically by heating sodium formate :



Oxalic acid and its alkaline salts are very soluble in water. Its calcium salts are insoluble in water and dilute acetic acid, but are soluble in the acid phosphates of the urine.

According to Lommel,<sup>4</sup> oxalic acid is a product of metabolism, and is not produced proportionally to proteid destroyed, but occurs in increased amounts in the urine when nucleins (thymus) and gelatin are fed. The occurrence of oxalic acid in the urine after feeding nucleins is significant in virtue of its possible origin from uric acid (see Uric Acid, p. 554). Stones in the bladder are sometimes composed of calcium oxalate, as are also urinary sediments when formed in consequence of ammoniacal fermentation.

**Succinic Acid,**  $\text{HOOC.C}_2\text{H}_4.\text{COOH}$ .—This has been detected in the spleen, thymus, thyroid, in echinococcus fluid, and often in hydrocele fluid. It is a product of alcoholic fermentation, and of proteid putrefaction. It is often found in plants.

**Amido-succinic Acid, or Aspartic Acid,**  $\text{HOOC.C}_2\text{H}_3\text{NH}_2.\text{COOH}$ . This is a product of boiling proteid with acid or alkalies, and it is also formed under the influence of trypsin in proteid digestion.

<sup>1</sup> Krüger and Salomon: *Zeitschrift für physiologische Chemie*, 1898, Bd. 26, S. 350.

<sup>2</sup> Krüger and Wulff: *Ibid.*, 1895, Bd. 20, S. 184.

<sup>3</sup> Boudzynski and Gottlieb, *Op. cit.*, S. 132.

<sup>4</sup> *Deutsches Archiv für klinische Medizin*, 1890, Bd. 63, S. 599.



**Monamide of Amido-succinic Acid, or Asparagin,  $H_2NOC.C_2H_4NH_2.COOH$ .**

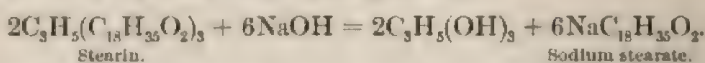
—This is found widely distributed in plants, especially in the germinating seed. If a plant be placed in the dark its proteid nitrogen decreases, whereas the non-proteid nitrogen increases,<sup>1</sup> the cause of this being attributed to proteid metabolism with the production of amido-acids, *i. e.* aspartic and glutamic acids, leucin, and tyrosin. In the sunlight, it is believed, these bodies are later reconverted into proteid. One view regarding the formation of asparagin is based theoretically on the production of succinic acid from carbohydrates (as in alcoholic fermentation) and the subsequent formation of *oxysuccinic acid* (or *malic acid*,  $HOOC.C_2H_4OH.COOH$ ), which the inorganic nitrogenous salts change to asparagin.<sup>2</sup> At any rate asparagin in the plant has the power of being constructed into proteid. Since proteid in the animal body may yield 60 per cent. of dextrose in its decomposition, as will be shown, it seems fair to surmise that the synthesis of proteid in the plant may in part depend upon the union of asparagin or similar amido-compounds with the carbohydrates present. Asparagin if fed is converted into urea. It forms no proteid synthesis in the animal, and has only a very small effect as a food-stuff.<sup>3</sup>

**Glutamic acid,  $HOOC.CHNH_2.CH_2.CH_2.COOH$ .**—This is found as a cleavage-product of tryptic digestion in the intestinal canal. *Glutamin*, its amido-compound, is, like asparagin, widely distributed in the vegetable kingdom and in considerable amounts. It probably plays the same rôle as asparagin in the plant. Glutamin is more soluble than asparagin and is therefore less easily detected.

**COMPOUNDS OF TRIATOMIC ALCOHOL RADICALS.**

**Glycerin, or Propenyl Alcohol,  $CH_2OH.CHOH.CH_2OH$ .** The glycerin esters of the fatty acids form the basis of all animal and vegetable fats. Glycerin is furthermore formed in small quantities in alcoholic fermentation.

*Preparation.*—(1) Through the action of an alkali on a fat, glycerin and a *sap* are formed, a process called *saponification*:



(2) Fats may be decomposed into glycerin and fatty acid by superheated steam, and likewise by the fat-splitting ferment in the pancreatic juice. Thus, if a thoroughly washed butter-ball, consisting of pure neutral fat, be colored with blue litmus, and a drop of pancreatic juice be placed upon it, the mass will gradually grow red in virtue of the fatty acid liberated from its glycerin combination. This reaction takes place in the intestine.

If fatty acid be fed, the chyle in the thoracic duct is found to contain much neutral fat.<sup>4</sup> This synthesis indicates the presence of glycerin in the body—perhaps, in this case, in the villus of the intestine: the source of this glycerin, whether from proteid or carbohydrates, is problematical. If glycerin be fed, only little is absorbed (since diarrhoea ensues), and of that little some appears in the urine. It seems, therefore, to be oxidized with difficulty in the body.

**Glycerin Aldehyde,  $HOCH_2.CHOH.CHO$ , and Dioxycetone,  $HOCH_2.CO.CH_2OH$ .**—These substances are formed by the careful oxidation of glycerin with nitric acid, and together are termed *glycerose*. They have a sweet taste and are the lowest known

<sup>1</sup> Schulze and Kisser: *Landwirthschaftliche Versuchs-Station*, 1889, Bd. 36, S. 1.

<sup>2</sup> Müller: *Ibid.*, 1886, Bd. 33, S. 326.

<sup>3</sup> See Voit: *Zeitschrift für Biologie*, 1892, Bd. 29, S. 125.

<sup>4</sup> Munk: *Virchow's Archiv*, 1880, Bd. 80, S. 17.

members of the glyucose (sugar) series—i. e. substances which are characterized by the presence of either aldehyde-alcohol,  $-\text{CHOH}-\text{CHO}$ , or ketone alcohol,  $-\text{CO}-\text{CH}_2\text{OH}$ , radicals. The constituents of glycerose, from the number of their carbon atoms, are called *trioses*. On boiling glycerose with barium hydrate the two constituents readily unite to form *D*-fructose (levulose).

**Glycerin Phosphoric Acid**,  $(\text{HO})_2\text{C}_3\text{H}_5\cdot\text{H}_2\text{PO}_4$ .—This is the only ethereal phosphoric acid in the urine. It is found in mere traces.

**Lecithin**,  $\text{C}_3\text{H}_5 \diagup (\text{C}_{20}\text{H}_{39}\text{O}_2)_2 \diagdown \text{O} \cdot \text{PO}(\text{OH}) \cdot \text{O} \cdot \text{C}_2\text{H}_4 \cdot \text{N}(\text{CH}_3)_3 \cdot \text{OH}$ .—Lecithin is found in every cell, animal or vegetable, and especially in the brain and nerves. It is found in egg-yolk, in muscles, in blood-corpuscles, in lymph, pus-cells, in bile, and in milk. On boiling lecithin with acids or alkalies, or through putrefaction in the intestinal canal, it breaks up into its constituents, fatty acids, glycerin phosphoric acid, and cholin (see p. 543), substances which the intestine may absorb. The fatty acids may be stearic, palmitic, or oleic, two molecules of different fatty acids sometimes uniting in one molecule of lecithin: hence there are varieties of lecithins. Through further putrefaction cholin breaks up into carbonic oxide, methane, and ammonia.<sup>1</sup> Lecithin treated with distilled water swells, furnishing the reason for the "myelin forms" of nervous tissue. Lecithin is readily soluble in alcohol and ether. It feels waxy to the touch. *Protagon*, which has been obtained especially from the brain, is a crystalline body containing lecithin and *cerebrin*—which is a glucoside (a body separable into proteid and a sugar). The chemical identity of protagon is shown in that ether and alcohol will not extract lecithin from it.<sup>2</sup> Protagon readily breaks up into its constituents. While protagon seems to be regarded as the principal form in which lecithin occurs in the brain, simple lecithin is believed to be present in the nerves and other organs. This subject has not been properly worked out. Noll<sup>3</sup> states that the quantity of protagon in the spinal cord may amount to 25 per cent. of the dry solids, in the brain to 22 per cent., and in the sciatic nerve to 7.5 per cent. Regarding the synthesis of lecithin in the body, or the physiological importance of the substance, absolutely nothing is known.

**FAT IN THE BODY**.—Animal and vegetable fats consist principally of a mixture of the triglycerides of palmitic, stearic, and oleic acids. In the intestines the fat-splitting ferments convert a small portion of fat into glycerin and fatty acid; the fatty acid unites with alkali to form a soap, in the presence of which the fat breaks up into fine globules called an *emulsion*; the fat-splitting ferment then acts further on the fat, probably converting it all into fatty acid and glycerin.<sup>4</sup> A fine emulsion of lanolin (fatty acid in combination with cholesterol, ischolesterin, etc.) is not absorbed, because the intestine does not break up the combination,<sup>5</sup> and the melted particles themselves cannot

<sup>1</sup> Hasebroek: *Zeitschrift für physiologische Chemie*, 1888, Bd. 12, S. 148.

<sup>2</sup> Gamgee and Blankenhorn: *Journal of Physiology*, 1881, vol. ii. p. 113.

<sup>3</sup> *Zeitschrift für physiologische Chemie*, 1899, Bd. 27, S. 370.

<sup>4</sup> Frank, O.: *Zeitschrift für Biologie*, 1898, Bd. 36, S. 568.

<sup>5</sup> Counstein: *Archiv für Physiologie*, 1899, S. 30.



be absorbed. When the fatty acids are produced they unite with the alkali of the intestines to form soaps. The solution of these soaps is greatly aided by the bile.<sup>1</sup> The tissue of the villus has the power to unite synthetically the absorbed soap and glycerin to form neutral fat.

It should be remembered that the changes necessary for the absorption of fat may also take place in a cleansed isolated loop of the intestine.<sup>2</sup>

Fat may likewise be derived from ingested carbohydrates. The chemical derivation of fatty acid from carbohydrates has already been mentioned in the case of formic, acetic, propionic (see p. 537), and butyric acids. The fatty acids of fusel oils are likewise formed from carbohydrates in fermentation. The laboratory synthesis of sugar from glycerin has been already related. These reactions, however, furnish only the smallest indication of the large transformation of carbohydrates into fat possible in the body.

If geese be fed with rice in large quantity, and the excreta and air respired be analyzed, it may be shown that carbon is retained in large amount by the body, in amount too great to be entirely due to the formation of glycogen, and must therefore have been deposited in the form of fat.<sup>3</sup> Such fattening of geese produces the delicate *pâté de foie gras*. The principle has been established in the case of the dog as well.<sup>4</sup>

The formation of fat from proteid (fatty degeneration) is believed to take place in some pathological cases (see p. 513). Recollection of the fact that proteid may yield 60 per cent. of sugar aids in the comprehension of this problem.<sup>5</sup>

Other usually cited proofs of the formation of fat from proteid include the conversion of casein into fat incident to the ripening of cheese; and the transformation of muscle in a damp locality into a cheese-like mass called *adipocere*, which is probably effected by bacteria.<sup>6</sup> Adipocere contains double the original quantity of fatty acid, occurring as calcium, and sometimes as ammonium salts.

Experiments of C. Voit show that on feeding large quantities of proteid, not all the carbonic acid is expired that belongs to the proteid destroyed as indicated by the nitrogen in the urine and feces. The conclusion follows that a non-nitrogenous substance has been stored in the body. Too much carbon is retained to be present only in the form of glycogen; fat from proteid must therefore have been stored.<sup>7</sup> The formation of fat normally from proteid has been combated by Pflüger, it would seem without proper foundation. For behavior of fat in the cell see p. 558.

**Oleic Acid,  $C_{18}H_{34}O_2$ .**—This acid belongs to the series of fatty acids having the formula  $C_nH_{2n-2}O_2$ . Its glyceride solidifies only as low as  $+4^\circ$  C. It is the principal compound of liquid oils. Pure stearin is solid at the body's temperature, but mixed with olein the melting-point of the mixture is reduced below the temperature of the body and its absorption is thereby rendered possible. The fat in the body is all in a fluid condition, due to the presence of olein.

<sup>1</sup> Moore and Rockwood: *Journal of Physiology*, 1897, vol. xxi. p. 58.

<sup>2</sup> Cunningham: *Ibid.*, 1898, vol. 23, p. 209.

<sup>3</sup> Voit: Abstract in *Jahresbericht über Thierchemie*, 1885, Bd. 15, S. 51.

<sup>4</sup> Rübner: *Zeitschrift für Biologie*, 1886, Bd. 22, S. 272.

<sup>5</sup> Ray, McDermott and Lusk: *American Journal of Physiology*, 1899, vol. 3, p. 139.

<sup>6</sup> Read Lehmann: Abstract in *Jahresbericht über Thierchemie*, 1889, Bd. 19, S. 516.

<sup>7</sup> Erwin Voit: *Münchener medicinische Wochenschrift*, No. 26, 1892; abstract in *Jahresbericht über Thierchemie*, 1892, S. 34; Cremer, M.: *Zeitschrift für Biologie*, 1899, Bd. 38, S. 309.

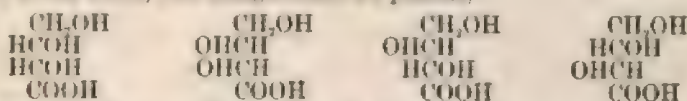
## CARBOHYDRATES.

The important sugar of the blood and the tissues is dextrose. It is derived from the hydration of starchy foods, and from proteid metabolism. From dextrose the lactic glands probably manufacture another carbohydrate, milk-sugar. Cane-sugar forms an article highly prized as a food. The study of the various sugars or carbohydrates is of especial interest, because their chemical nature is now well known.

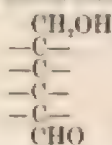
Carbohydrates were formerly defined as bodies which, like the sugars and substances of allied constitution, contain carbon, hydrogen, and oxygen, the carbon atoms being present to the number of six or multiples thereof, the hydrogen and oxygen being present in a proportion to form water. *Glycoses* include the monosaccharides like dextrose,  $C_6H_{12}O_6$ ; *disaccharides* include, for example, cane-sugar,  $C_{12}H_{22}O_{11}$ , which breaks up into dextrose and levulose, while *polysaccharides* comprise such bodies as starch and dextrins, which have the formula  $(C_6H_{10}O_5)_n$ .

In recent years the term glycose has been extended to cover bodies having three to nine carbon atoms and possessing either the constitution of an aldehyde-alcohol,  $-CH(OH)CHO$ , called *aldoses*, or of a ketone-alcohol,  $-COCH_2OH$ , called *ketoses*. These bodies also have hydrogen and oxygen present in a proportion to form water, and the number of carbon atoms always equals in number those of oxygen. According to their number of carbon atoms they are termed trioses, tetroses, pentoses, hexoses, heptoses, octoses, and nonoses.

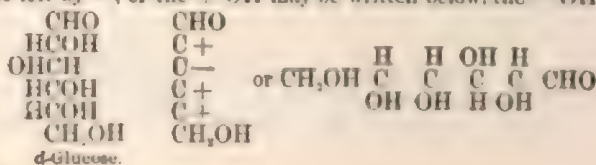
It has been shown (foot-note, p. 545) how from the asymmetric carbon atom in lactic acid two configurations are derived. If a body (such as trioxibutyric acid) contains two asymmetric carbon atoms, four configurations are possible,



Similarly among the glucose-aldoses, a triose has two modifications; a tetrose, four; a pentose, eight; a hexose, sixteen, etc. Thus in the following formula by the variations of H and OH on the four asymmetric carbon atoms, sixteen possible hexoses may be obtained.



The carbohydrates have well-defined optical properties, rotating polarized light to the right or left, and were therefore originally designated as *d*-(dextro-) and *l*-(laevo-) respectively. An inactive (*i*) form consists in an equal mixture of the two others; at present, however, the *d*- may signify a chemical relation to dextrose: thus levulose, which is ordinary fruit sugar and rotates polarized light to the left, is called *d*-fructose, on account of its derivation from dextrose. Where the OH group is attached on the right it may be indicated by the sign +, on the left by —, or the + OH may be written below, the — OH above.



*d*-Glucose.



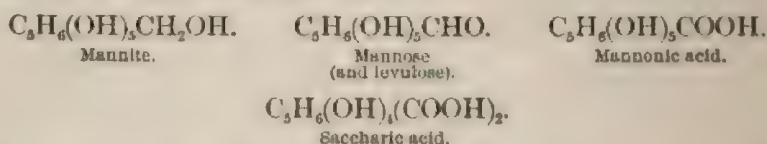
## THE GLYCOSES.

The triose called glycerose has already been described.

A tetrose called *erythrose*, which is the aldose of erythrite,  $C_4H_6(OH)_4$ , a tetratomic alcohol, is known.

Of the possible pentoses, *arabinose*, *xylose*, and *rhamnose* (methyl-arabinose) occur in the vegetable kingdoms in considerable quantity. They may be absorbed by the intestinal canal.<sup>1</sup> Pentoses are found in the urine in rare cases.<sup>2</sup> Some nucleins, especially those of the pancreas and thymus, yield pentoses on decomposition. Subcutaneous injection of arabinose, xylose, and rhamnose results in their excretion to the extent of more than 50 per cent. in the urine.<sup>3</sup> The rest may be burned.

**Hexoses, or Glucoses.**—Through the oxidation of hexatomic alcohols there may be obtained, first, glucoses, then monocarbonic acids, and lastly saccharic acid, or its isomer mucic acid:

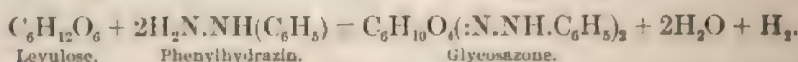


*Mannose* and *levulose* are respectively the aldose and ketose of mannite, *galactose* is the aldose of dulcitate, whereas *glucose* is probably the aldose of sorbite—dulcitate and sorbite being, like mannite, hexatomic alcohols.

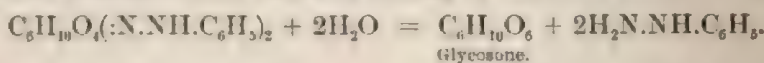
**Properties.**—(1) The hexoses are converted into their respective alcohols on reduction with sodium amalgam.

(2) The hexoses act as reducing agents, converting alkaline solutions of cuprous oxide salts (obtained through presence of tartrate) into red cuprous oxide, which precipitates out (Trommer's test). Levulic acid is among the products formed (see p. 538). Of the higher saccharides only maltose and milk-sugar give this reaction.

(3) Strongly characteristic are the insoluble crystalline compounds formed by all glycoses with phenylhydrazin, called *osazones* (see p. 534):



Levulose, dextrose, and mannose give the same glycosazone. The glycosazones are decomposed into osones by fuming hydrochloric acid:



Osones are converted into sugar by nascent hydrogen. The osone derived from levulose, dextrose, and mannose yields levulose by this treatment, and the transformation of dextrose and mannose into levulose is therefore demonstrated.

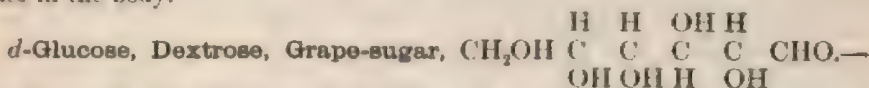
<sup>1</sup> Weiske: *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, S. 489.

<sup>2</sup> Salkowski: *Zeitschrift für physiologische Chemie*, 1899, Bd. 27, S. 507.

<sup>3</sup> Voit, F.: *Deutsches Archiv für klinische Medizin*, Bd. 58, S. 523.

(4) Only trioses, hexoses, and nonoses are capable of alcoholic fermentation.

*Synthesis of the Glucoses.*—Formose (see p. 533) may be purified by means of phenylhydrazin as above, so that pure *i*-fructose is obtained; this treated with sodium amalgam yields *i*-mannite, which on oxidation is converted into *i*-mannonic acid; this last is separated by a strychnin salt into its two components; the *d*-mannonic acid is divided and one part treated with hydrogen, with resulting *d*-mannose, which, as has been shown above, is convertible into *d*-fructose or ordinary fruit-sugar; the second part of the *d*-mannonic acid treated with chinolin is transformed through change in configuration into its isomer, *d*-gluconic acid, which on reduction yields *d*-glucose, or ordinary dextrose. This shows the preparation of the common sugars from their elements. The transformation of levulose into dextrose is especially to be noted, since it takes place in the body.



This is the sugar of the body. It is found in the blood and other fluids and in the tissues to the extent of 0.1 per cent. and more, even during starvation. The principal source of the dextrose of the blood is that derived from the digestion of starch, and also of cane-sugar, in the intestinal tract. Dextrose is likewise produced from proteid, for a diabetic patient fed solely on proteid may still excrete sugar in the urine. Minkowski<sup>1</sup> finds that in starving dogs after extirpation of the pancreas the proportion of sugar to nitrogen is 2.8 : 1. The same ratio has been shown to exist in phlorhizin diabetes in fasting rabbits<sup>2</sup> and goats<sup>3</sup> when the drug is frequently administered. After frequent dosage of phlorhizin to fasting, meat-fed, or gelatin-fed dogs, the ratio dextrose : nitrogen approximates 3.75 : 1. Since 1 gram of N in the urine corresponds (neglecting the faecal N) to 6.25 grams of proteid destroyed, therefore, 3.75 grams of sugar must have arisen from 6.25 grams of proteid (including gelatin). In other words, there has been a production from the proteid molecule of 60 per cent. of dextrose, which contains nearly 60 per cent. of the physiologically available energy of the proteid consumed.<sup>4</sup> A similar large excretion of dextrose has been noted in cases of human *diabetes mellitus*.<sup>5</sup>

In pancreas diabetes the pancreas may perhaps manufacture a ferment which, supplied from the lymph of the pancreas<sup>6</sup> to the tissues, becomes the first cause of the decomposition of dextrose, and in whose absence diabetes ensues. Excess of dextrose in the body is stored up, especially in the liver-cells, as *glycogen*, which is the anhydride of dextrose; the glycogen may be afterwards reconverted into dextrose. The presence of sugar in the body in starvation, even when little urea may be detected there, shows the readier excre-

<sup>1</sup> *Archiv für Exper. Pathologie und Pharmacologie*, 1893, Bd. 31, S. 85.

<sup>2</sup> Lusk : *Zeitschrift für Biologie*, 1898, Bd. 36, S. 82.

<sup>3</sup> Lusk : Unpublished.

<sup>4</sup> Reilly, Nolan, and Lusk : *American Journal of Physiology*, 1898, vol. i. p. 395.

<sup>5</sup> Rumpf : *Berliner klinische Wochenschrift*, 1898, Bd. 24, Heft 43.

<sup>6</sup> Biedl : *Centralblatt für Physiologie*, 1898, Bd. 12, S. 624.

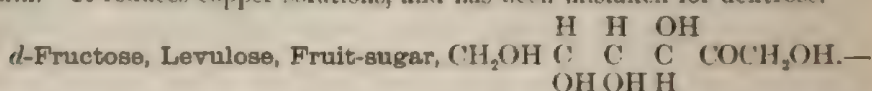


tion of the nitrogenous radical of proteid. Traces of dextrose are found in normal urine.

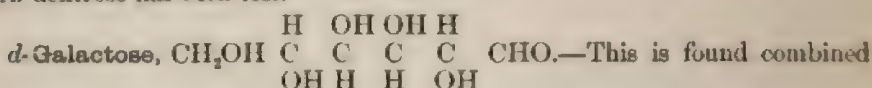
Dextrose is a sweet-tasting crystalline substance; its solutions rotate polarized light to the right.

Jecorin, a substance found in the liver and the blood, yields dextrose on decomposition. It is said to be a glycose-lecithin.<sup>1</sup>

Glucosamin,  $C_6H_{11}O_5NH_2$ .—This is yielded as a decomposition product of some proteids. Egg albumin, for example, yields 8 per cent. of glucosamin. It reduces copper solutions, and has been mistaken for dextrose.



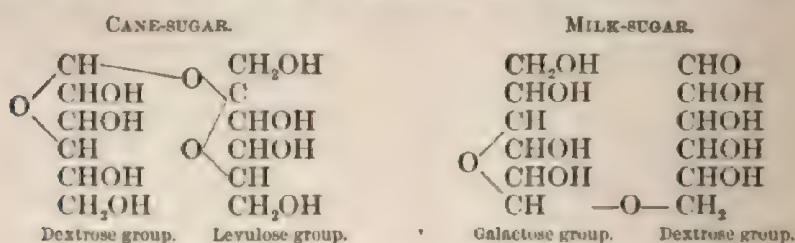
This occurs in many fruits and in honey. It is sweeter than dextrose, and rotates polarized light to the left. It is a product of the decomposition of cane-sugar in the intestinal canal. If levulose be fed, any excess in the blood may be converted into glycogen, and through the glycogen into dextrose. It is possible thus to convert 50 per cent. of the levulose fed into dextrose.<sup>2</sup> When levulose is fed to a diabetic patient, it may be burned, though power to burn dextrose has been lost.<sup>3</sup>



with proteid in the brain, forming the glucoside cerebrin. It is produced together with dextrose in the hydrolytic decomposition of milk-sugar. It does not undergo alcoholic fermentation, at least not with *Saccharomyces apiculatus*. When fed it may in part be directly burned or in part converted into glycogen.

#### THE DISACCHARIDES, $C_{12}H_{22}O_{11}$ .

These are di-multiple sugars in ether-like combination. To cane-sugar and milk-sugar, Fisher has ascribed the following formulæ:<sup>4</sup>



**Cane-sugar, or Saccharose.**—Cane-sugar, obtained from the sugar-cane and the beet-root, is largely used to flavor the food, and likewise assumes importance as a food-stuff. On boiling with dilute acids, cane-sugar is converted through hydrolysis into a mixture of levulose and dextrose. The same

<sup>1</sup> Bing: *Centralblatt für Physiologie*, 1893, Bd. 12, S. 209.

<sup>2</sup> Minkowski: *Archiv für Pathologie und Pharmakologie*, 1893, Bd. 31, S. 157.

<sup>3</sup> *Loc. cit.*

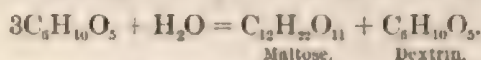
<sup>4</sup> *Berichte der deutschen chemischen Gesellschaft*, 1894, Bd. 26, S. 2400.

result is obtained by warming with 0.05 to 0.2 per cent. hydrochloric acid at the temperature of the body.<sup>1</sup> This inversion, therefore, takes place in the stomach. In the intestinal canal the inversion is accomplished through the action of a ferment present in the intestinal juice. Subcutaneous injection of cane-sugar results in its quantitative excretion through the urine;<sup>2</sup> but fed *per os*, cane-sugar is converted into dextrose and levulose, which may be burned in the body.

**Milk-sugar, or Lactose.**—This is found in the milk and in the amniotic fluid. It is probably manufactured from dextrose in the mammary glands, for the blood does not contain it. It is always present in the urine during the first days of lactation, but is not found there *ante-partum*.<sup>3</sup> It readily undergoes lactic fermentation, producing lactic acid, which then causes clotting of the milk. This fermentation may take place in the intestinal tract. Boiling with dilute acids splits up milk-sugar into galactose and dextrose. This decomposition probably does not take place in the stomach. The intestinal juice causes this transformation, especially in suckling animals,<sup>4</sup> and lactase of the pancreatic juice will also split milk-sugar.<sup>5</sup> Milk-sugar injected subcutaneously in man is quantitatively eliminated through the kidney.<sup>6</sup> It must, therefore, undergo inversion in the intestine into galactose and dextrose before it can be burned.

**Isomaltose.**—This is the only disaccharide which has been synthetically obtained, having been produced by boiling dextrose with hydrochloric acid. It ferments with difficulty and forms an osazone which melts at 150°–153°. It, with dextrin, is a product of the action of diastase and of the diastatic enzymes found in saliva, pancreatic juice, intestinal juice, and blood upon starch and glycogen. Through further action of the same ferments isomaltose is converted into maltose.

**Maltose.**—Maltose (and dextrin) are the end-products of the action of diastase on starch and glycogen, the process being one of hydrolysis:



It is likewise a product of the diastatic action of ptyalin (saliva), amylopsin (pancreatic juice), and of ferments in the intestinal juice and in the blood. Maltose readily undergoes alcoholic fermentation and forms an osazone which melts at 206°. It is converted into dextrose by boiling with acids. Certain ferments convert maltose (and dextrin) into dextrose (see Starch).

#### CELLULOSE GROUP, $(\text{C}_6\text{H}_{10}\text{O}_5)_n$ .

**Cellulose.**—This is a highly polymerized anhydride of dextrose, perhaps also of mannose. It forms the cell-wall in the plant. It undergoes putrefaction in the intestinal

<sup>1</sup> Ferris and Lusk: *American Journal of Physiology*, 1898, vol. 1, p. 277.

<sup>2</sup> Voit, F.: *Deutsches Archiv für klinische Medizin*, 1897, Bd. 58, S. 523.

<sup>3</sup> Lemaire: *Zeitschrift für physiologische Chemie*, 1896, Bd. 10, S. 442.

<sup>4</sup> Weinland: *Zeitschrift für Biologie*, 1899, Bd. 38, S. 16.

<sup>5</sup> *Ibid.*, 1899, Bd. 38, S. 607.

<sup>6</sup> Voit, F.: *Loc. cit*



canal, especially in herbivora (see p. 532), and owing to the production of fatty acids it may have value as a food. In man only young and tender cellulose is digested, such as occurs in lettuce and celery. The bulk of herbivorous fecal matter consists of cellulose. Cellulose is only with difficulty attacked by acids and alkalies. Tunicin, found among the tunicates, is identical with cellulose, so that the substance is not solely characteristic of the vegetable kingdom.

**Starch,**  $(C_6H_{10}O_5)_{20}$ .—This substance on boiling with dilute acids breaks down by hydrolysis principally to dextrose. It is found in plants, and may be manufactured by them from cane-sugar, dextrose, levulose, and from other sugars. It forms a reserve food-stuff, being converted into sugar as the plant requires it—in winter, for example. Starch gives a blue color with iodine. According to recent investigations<sup>1</sup> starch is said to be broken up by diastase into five successive hydrolytic cleavage-products as follows: (1) *Amylodextrin*  $(C_{12}H_{20}O_{10})_{34}$ , a substance giving a deep-blue color with iodine. This is next changed to (2) *Erythrodextrin*,  $(C_{12}H_{20}O_{10})_{13} + H_2O$ , or  $(C_{12}H_{20}O_{10})_{17}$ ,  $(C_{12}H_{22}O_{11})$ , which is readily soluble in water and gives with iodine a reddish-brown color. Erythrodextrin is converted into (3) *Achrodextrin*,  $(C_{12}H_{20}O_{10})_6 + H_2O$ , or  $(C_{12}H_{20}O_{10})_5 \cdot C_{12}H_{22}O_{11}$ , which is likewise very soluble, tastes slightly sweet, but gives no coloration with iodine. Achrodextrin now breaks up into (4) *Isomaltose*, which through change in configuration is transformed to its isomere (5) *Maltose*.

Products similar to these are formed by the various diastatic ferments in the body, and in addition also some dextrose. Ptyalin<sup>2</sup> acts rapidly on starch, producing dextrin and maltose, but very little dextrose. Amylopsin, from the pancreas, acts still more rapidly than ptyalin, and with the production of considerable dextrose. The diastatic ferment of intestinal juice acts very slowly on starch, forming dextrin, maltose, and a little dextrose, while the ferment in blood-serum likewise acts slowly but with complete transformation of all the maltose and dextrin formed, into dextrose.

The above facts lead Hamburger to suggest that the diastatic ferments of the body consist of mixtures, in different proportions, of diastase, which forms dextrin and maltose from starch, and of glucase, which converts these into dextrose. This, however, is merely an hypothesis, and glucase has never been prepared. The vegetable diastase is not identical with that found in the body. Thus ptyalin, like emulsin, breaks up salicin into salicylic alcohol and dextrose, of which action vegetable diastase is incapable. But ptyalin, again, is not identical with emulsin, for it will not act on amygdalin.

The subcutaneous injection of solutions of achrodextrin, erythrodextrin, and amylo-dextrin results in their partial elimination in the urine, the rest being burned.<sup>3</sup>

**Glycogen, or Animal Starch.**—Recent investigations have shown that in all the particulars of diastatic decomposition glycogen is identical with vegetable starch.<sup>4</sup> Glycogen is soluble in water, giving an opalescent fluid. The blood has a normal composition which does not greatly vary. After a hearty meal excess of fat is deposited in fatty tissue, excess of proteid in the muscular

<sup>1</sup> Lintner und Düll: *Berichte der deutschen chemischen Gesellschaft*, 1893, Bd. 26, S. 2533.

<sup>2</sup> See Hamburger: *Pflüger's Archiv*, 1895, Bd. 60, S. 573.

<sup>3</sup> Voit, F.: *Deutsches Archiv für klinische Medizin*, Bd. 43, S. 523.

<sup>4</sup> Külz and Vogel: *Zeitschrift für Biologie*, 1895, Bd. 31, S. 108.

tissue, while excess of sugar is stored in the muscles and especially in the liver-cells in the less combustible and less diffusible form of glycogen. About one-half of the total quantity of glycogen is found in the muscles, the remainder in the liver, where it may even amount to 40 per cent. of the dry solids. When the blood becomes poor in sugar, the store of glycogen is drawn upon to such an extent that in hunger the body loses the larger part of its glycogen. Muscular work likewise causes the rapid conversion of glycogen into sugar. The sources of glycogen are certain ingested carbohydrates, and also the dextrose derived from proteid. If large quantities of proteid be fed, glycogen may be stored. If dextrose, levulose, or galactose (or anything which produces these, *e. g.* cane-sugar, maltose, milk-sugar) be fed, there may be a direct conversion of these sugars into glycogen. Cremer maintains that the pentoses are burned in the body, but are only indirectly glycogen-producers in the sense of sparing other sugar from destruction, which may be used to form glycogen.

**Dextrins.**—These have been described under starch.

***d*-Glucuronic Acid, or Glycuronic Acid,**  $\begin{array}{ccccccc} & \text{H} & \text{H} & \text{OH} & \text{H} & & \\ & | & | & | & | & & \\ \text{HOOC} & \text{C} & \text{C} & \text{C} & \text{C} & \text{CHO.} \\ & | & | & | & | & & \\ & \text{OH} & \text{OH} & \text{H} & \text{OH} & & \end{array}$

—Obtained by reducing *d*-saccharic acid with nascent hydrogen. After feeding chloral hydrate, naphthalin, camphor, terpentine, phenol, ortho-nitrotoluol, and other bodies, they appear in the urine (usually having been first converted into alcohol) in combination with glycuronic acid. Urochloralic acid, naphthol-glycuronic acid, campho-glycuronic acid, terpene-glycuronic acid, etc., all rotate polarized light to the left. It seems that these ingested substances unite in the body with the aldehyde group of dextrose, at the same time protecting all but one group of the dextrose molecule from further oxidation (Fischer). Glycuronic acid, which is easily separated by hydrolysis from its aromatic combination, itself rotates polarized light to the right, reduces alkaline copper solutions, and might be confounded with dextrose except that it does not ferment with yeast. Glycuronic acid is likewise found in the urine after administration of curare, morphine, and after chloroform-narcosis, perhaps paired with aromatic bodies formed in the organization.

**COMBUSTION IN THE CELL IN GENERAL.**—Experiments<sup>1</sup> show that taking the proteid decomposition in the starving dog as 1, it is necessary to feed three to four times that amount of proteid taken alone in order to attain nitrogenous equilibrium, 1.6 to 2.1 times that amount of proteid when fed with fat, and 1 to 1.2 times that amount when fed with carbohydrates. The physiological proteid minimum is in these cases never less than the amount required in starvation. Only after feeding gelatin with proteid may the proteid fed be below the amount decomposed in starvation. The above shows what is well known, that sugar spares proteid from decomposition more than fat does. E. Voit<sup>2</sup> states

<sup>1</sup> E. Voit and Korkunoff: *Zeitschrift für Biologie*, 1895, Bd. 32, S. 117.

<sup>2</sup> *Op. cit.*, S. 128 and 135.



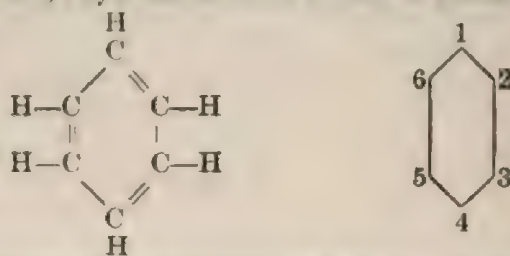
these two propositions: (1) The part played by these several food-stuffs in the total metabolism depends on the composition of the fluid feeding the cell. The greater the amount of one of these food-stuffs, the greater its decomposition and the less the decomposition of the others, so long as the total decomposition suffers no change. (2) The several food-stuffs do not act wholly on account of their quantity in the fluid surrounding the cell, but especially according to the chemical affinity of the cell-substance for them individually. First in this regard comes proteid, then carbohydrates, and lastly fat.

The excessive proteid decomposition in diabetes is due to the non-combustion of the proteid protecting sugars,<sup>1</sup> and the same is in part true in fever, where a small supply of carbohydrates reaches the blood.<sup>2</sup> Dextrose and levulose weight for weight have equal value in protecting proteid metabolism.<sup>3</sup>

For further discussion of carbohydrates in the body see under the individual sugars, and under Fat in the Body.

#### BENZOL DERIVATIVES OR AROMATIC COMPOUNDS.

The aromatic compounds are characterized by a configuration in which six atoms of carbon are linked together in a circle called the benzol ring. The type of this is benzol, a hydrocarbon found in coal-tar and having the formula,



The hydrogen atoms may be substituted by others, substitution of one OH group, for example, forming phenol,  $C_6H_5-OH$ . If, however, two OH groups are substituted, three different bodies, corresponding to the different arrangements on the ring, become possible. If the two OH groups occupy the positions 1 and 2 the substance is *ortho*-dioxymenzol; if 1 and 3, *meta*-dioxymenzol; and if 1 and 4, *para*-dioxymenzol.

It is possible to convert bodies of the fatty series into those of the aromatic. Acetylene passed through red-hot tubes yields benzol. On the other hand, aromatic bodies may be converted into those of the fatty series. If phenol in aqueous solution be subjected to electrolysis by an alternating current under which circumstances hydrogen and oxygen are alternately liberated on the same pole, the effect of this intermittent oxidation and reduction is to break up the phenol into caproic acid, and finally, after passing through acids of lower carbon contents, into carbonic acid and water.

The aromatic compounds found in the urine are normally exclusively

<sup>1</sup> Lusk: *Zeitschrift für Biologie*, 1890, Bd. 27, S. 459.

<sup>2</sup> May: *Ibid.*, 1894, Bd. 30, S. 1.

<sup>3</sup> De Renzi und Realis: *VII. Congress für innere Medizin*, 1896.

derived from the products of proteid putrefaction in the intestines. It is admitted that neither fats nor carbohydrates play any part in their formation.

**Benzol**,  $C_6H_6$ .—This body if fed is absorbed and afterward converted into oxybenzol or phenol, with subsequent behavior similar to phenol.

**Phenol** (**Carbolic Acid**, **Oxybenzol**, **Phenyl-hydroxide**),  $C_6H_5OH$ .—This is an aromatic alcohol. A 5 per cent. solution precipitates proteid, and a much weaker solution produces irritation of the tissues, and especially those of the kidney, where its excretion takes place. It is strange that a strong antiseptic like phenol should be a normal product of proteid putrefaction. Phenol is obtainable from tyrosin, by processes of cleavage and oxidation (see Tyrosin), and in the intestinal canal is probably derived from tyrosin. A small amount of the phenol ordinarily absorbed is converted by the organism into pyrocatechin, a dioxybenzol. These two substances are found in normal urine in ethereal combination with sulphuric acid,  $C_6H_5O.SO_2.OH$  (or as an alkaline ethereal sulphate). This synthesis, accomplished by the union of the phenol and sulphuric acid with loss of water, has been obtained by electrolysis, using alternating electric currents.<sup>1</sup> If phenol be administered in more than a very small amount, hydroquinone likewise appears in the urine, paired like the others with sulphuric acid, and should the phenol administered exceed at any time the available sulphate, it forms to a certain extent a synthesis with glycuronic acid, and so combined appears in the urine.

Phenol gives with Millon's reagent (mercuric nitrate in nitric acid with some nitrous acid) a brilliant red coloration. This is given by all bodies having an hydroxyl group on the benzol ring, of which substance tyrosin may be mentioned as an example. It is likewise given by proteid, slowly in the cold, more rapidly on warming, and this fact together with the cleavage putrefactive products has given foundation to the belief that the oxybenzol ring exists preformed in the proteid molecule.

**Pyrocatechin**,  $C_6H_4(OH)_2$ .—This is ortho-dioxybenzol. For its formation see under Phenol.

**Hydroquinone**,  $C_6H_4(OH)_2$ .—Para-dioxybenzol. Found in the urine, especially in cases of carbolic-acid poisoning (see Phenol). If such urine be shaken in the air, it is turned black, owing to the oxidation of hydroquinone

to quinone,  $C_6H_4 \begin{smallmatrix} \diagup O \\ | \\ \diagdown O \end{smallmatrix}$ .

**p-Cresol**,  $C_6H_4.OH.CH_3$ .—This is a product of intestinal putrefaction, and is derived from tyrosin (which see). It is found in the urine as an ethereal sulphate.

**Benzoic Acid**,  $C_6H_5COOH$ .—Salts of this acid and analogous bodies are found especially in plants. In the urine of herbivora therefore is found a considerable amount of *hippuric acid*,  $COOH.CH_2.NH.CO.C_6H_5$ , the combination of benzoic acid and glycocoll (see Glycocoll, p. 537). On feeding *phenyl-acetic acid*,  $C_6H_5CH_2COOH$ , phenaceturic acid,  $COOH.CH_2.NH.CO.CH_2.C_6H_5$ , appears in the urine, while the higher benzyl acids, such as *phenyl-propionic acid*, suffer the oxidation of the side chain in the body, and

<sup>1</sup> Drechsel: *Journal für praktische Chemie*, Bd. 29, p. 229; abstr. *Jahresbericht über Thierchemie*, 1884, S. 77.

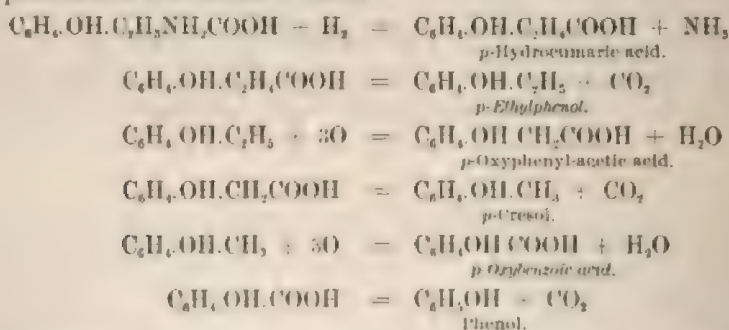


ordinary hippuric acid is formed. After eating apple-parings and other vegetable substances, hippuric acid is found in human urine. It is further stated that phenyl-acetic acid and phenyl-propionic acids are normal products of proteid putrefaction, though in very small quantities; hippuric acid and phenaceturic acid must therefore be constantly present in traces in human urine. Hippuric acid is split into its constituents by hydrolysis through the action of the *Micrococcus ureæ*.

***p*-Oxyphenyl-acetic Acid**,  $C_6H_4.OH.CH_2COOH$ .—This is a product of the intestinal putrefaction of proteid and of tyrosin (which see). It occurs in the urine either paired with sulphuric acid or as an alkaline salt of oxyphenyl-acetic acid.<sup>1</sup>

***p*-Hydrocumaric Acid**,  $C_6H_4.OH.C_2H_4COOH$ .—This second oxy-acid is likewise derived from proteid and tyrosin (which see) putrefaction. Its occurrence in the urine is similar to the above oxy-acid.

**Tyrosin, Amido-hydrocumaric Acid, *p*-Oxyphenyl-amido-propionic Acid**,  $C_6H_4.OH.C_2H_3NH_2COOH$ .—Tyrosin is a constant product of the putrefaction of all proteid bodies (except gelatin), and is therefore found in cheese. It may be formed in large quantities by boiling horn-shavings with sulphuric acid. Leucin is always formed whenever tyrosin is. Tyrosin forms characteristic sheaf-shaped bundles of crystals. All the aromatic bodies thus far described have been eliminated in the urine with their benzol nucleus intact. Tyrosin, however, may be completely burned in the body. This seems to be because of the presence of the amido-group on the side chain, for phenyl-amido-propionic acid is likewise destroyed. Tyrosin is found in the urine in yellow atrophy of the liver, in phosphorus-poisoning, etc. (see Leucin, p. 540). Through cleavage, oxidation, or reduction, the following reactions take place, phenol being the final product.<sup>2</sup> The substances not found in intestinal putrefaction are named in italics:



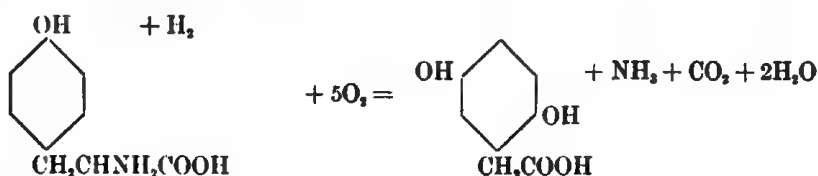
It has never been shown that tyrosin is a normal product of proteid metabolism within the tissues. With leucin it is a normal product of pancreatic digestion (see p. 540).

**Homogentisic Acid, Dioxypheyl-acetic Acid, Hydroquinone-acetic Acid**.—This is found in the urine in alcaptonuria. Feeding tyrosin in this disease increases the

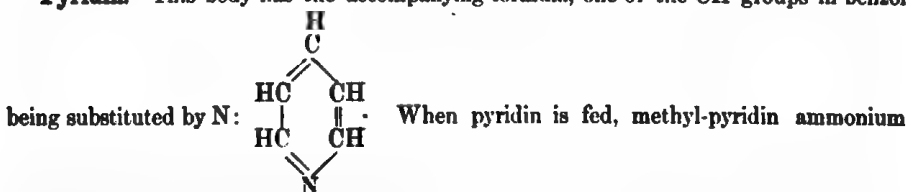
<sup>1</sup> Baumann: *Zeitschrift für physiologische Chemie*, 1886, Bd. 10, S. 125.

<sup>2</sup> Baumann: *Berichte der deutschen chemischen Gesellschaft*, 1879, Bd. 12, S. 1450.

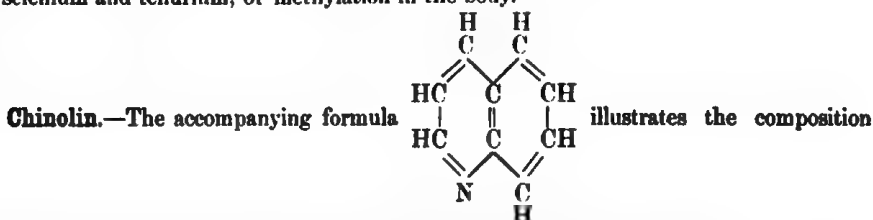
amount of homogentisic acid. It may arise from the reduction and oxidation of tyrosin according to the following reaction:<sup>1</sup>



**Pyridin.**—This body has the accompanying formula, one of the CH groups in benzol



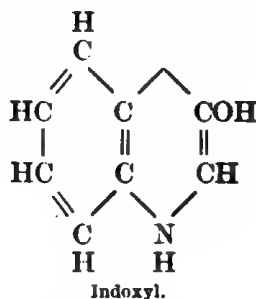
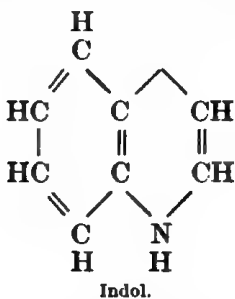
hydroxide,  $\text{OH}\cdot\text{CH}_3\cdot\text{NC}_5\text{H}_5$ , is excreted in the urine.<sup>2</sup> This is another case, besides those of selenium and tellurium, of methylation in the body.



of this body. Several of the methyl-chinolins burn readily in the body.<sup>3</sup>

**Cynurenic Acid**,  $\text{C}_8\text{H}_5\text{N}\cdot\text{OH}\cdot\text{COOH}$ .—This is oxychinolin carbonic acid; it is found normally in dog's urine, being derived from proteid in amounts proportional to proteid metabolism. It is, however, not derived from the metabolism of gelatin,<sup>4</sup> a body which does not yield the aromatic chain.

**Indol**, or **Benzopyrol**,  $\text{C}_8\text{H}_7\text{N}$ .—The source of indol is surely from proteid putrefaction; it may also be obtained by melting proteid with potash.



After its absorption it receives an oxy-group just as benzol does, and like benzol pairs with sulphuric acid with the loss of a molecule of water, and appears as ethereal sulphate in the urine. In preparing indol from feces the fecal odor clings to it. Pure indol, however, has no smell. An alcoholic

<sup>1</sup> Embden: *Zeitschrift für physiologische Chemie*, 1892, Bd. 17, S. 182.

<sup>2</sup> His: *Archiv für exper. Pathologie und Pharmacologie*, 1887, Bd. 22, S. 253.

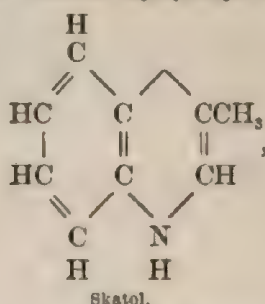
<sup>3</sup> Cohn: *Zeitschrift für physiologische Chemie*, 1894, Bd. 20, S. 210.

<sup>4</sup> Mendel and Jackson: *American Journal of Physiology*, 1899, vol. ii. p. 1.

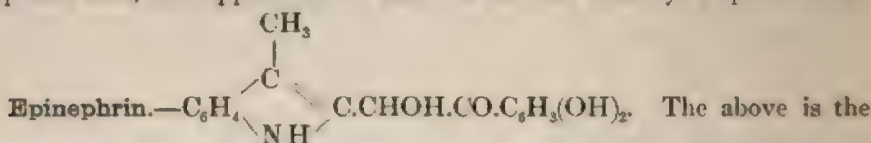


solution of indol mixed with hydrochloric acid colors fir-wood cherry-red. If urine be mixed with an equal volume of hydrochloric acid, chloroform added, and then gradually an oxidizing agent (chloride of lime), any indoxyl-sulphuric acid present will be oxidized to indigo-blue, which gives a blue color to the chloroform in which it dissolves.

**Skatol, or  $\beta$ -Methyl Indol,  $C_8H_7CH_3NH$ .**—The history of skatol,



is the same as that of indol. Its source is from proteid putrefaction; after absorption it unites with an oxy-group, and the skatoxyl thus produced pairs with sulphuric acid, and appears in the urine as ethereal skatoxyl-sulphuric acid.



formula for epinephrin, the active principle of the suprarenals, as proposed by Abel.<sup>1</sup> Abel has formed several distinct salts of this pyrrol base. Of the sulphate of epinephrin, only 0.000018 gram per kilogram of dog causes a sharp rise in blood-pressure.

**AROMATIC BODIES IN THE URINE.**—There have been named above as appearing in normal human urine the ethereal sulphates of phenol, *p*-cresol, pyrocatechin, indoxyl, skatoxyl, hydroparacumaric acid, and oxyphenyl-acetic acid, of which, however, the last two appear likewise as their salts without being combined with sulphuric acid.<sup>2</sup> These are derived from proteid putrefactive products formed almost entirely in the large intestine (see p. 545), which are partially absorbed and partially pass into the feces. The amount of ethereal sulphate in the urine gives an indication of the amount of intestinal putrefaction. It does not disappear in starvation, mucin and nucleoproteid of bile and intestinal juice furnishing material.<sup>3</sup> If the intestinal tract be treated so as to make it antiseptic, the ethereal sulphates disappear from the urine.<sup>4</sup> Diarrhoea likewise decreases their amount, obviously from the short time given for putrefaction. The synthesis between the aromatic bodies and sulphuric acid probably occurs in the liver. The liver and the kidney both have the power of combining with a considerable amount of

<sup>1</sup> *Zeitschrift für physiologische Chemie*, 1899, Bd. 28, S. 318.

<sup>2</sup> Baumann: *Zeitschrift für physiologische Chemie*, 1896, Bd. 10, S. 125.

<sup>3</sup> Von Noorden: *Pathologie des Stoffwechsels*, 1893, S. 163.

<sup>4</sup> Baumann: *Op. cit.*, S. 129.

indol and phenol, holding them until the requisite synthesis between them and sulphuric acid occurs, and thereby rendering them non-poisonous.<sup>1</sup>

**Inosit.**—This is the hexatomic phenol of hexahydrobenzol,  $C_6H_6(OH)_6$ . It was long mistaken for a carbohydrate. It has been found in muscle, liver, spleen, suprarenals, lungs, brain, and testicles; likewise in plants, in unripe peas and beans. After drinking much water it may be washed out in the urine, and perhaps for this reason is often found in the voluminous urine of the diabetic. When fed it is burned; also by the diabetic. Its origin is unknown.

#### SUBSTANCES OF UNKNOWN COMPOSITION.

##### COLORING MATTERS IN THE BODY.

**Hæmoglobin**,  $C_{712}H_{1130}N_{214}FeS_2O_{245}$  (Zinoffsky's formula for hæmoglobin in horse's blood).—Hæmoglobin is found in the red blood-corpuscle, probably in chemical union with the stroma.<sup>2</sup> United with oxygen it forms oxyhæmoglobin, which gives the scarlet color to arterial blood; hæmoglobin itself is darker, more bluish, and therefore venous blood is of a less brilliant red. Methods for preparing oxyhæmoglobin crystals are numerous, but all depend on getting the hæmoglobin into solution. If the corpuscles in error be washed with physiological salt-solution, and then treated with distilled water, the HbO will be dissolved; on shaking with a little ether the stroma will likewise dissolve; after decantation and evaporation of the ether, at the room's temperature, the solution is cooled to  $-10^\circ$  and a one-fourth volume of alcohol at the same temperature added; after a few days rhombic crystals of oxyhæmoglobin may be collected, redissolved in water, and reprecipitated for purification. The crystals may be dried *in vacuo* over sulphuric acid. Once dry they may be heated to  $100^\circ$  without decomposition, but in aqueous solution they are decomposed at  $70^\circ$  into a globulin and hæmatin, the latter having a brown color. This difference in color gives the distinction between "rare" and "well-done" roast-beef. Gastric and pancreatic digestion likewise converts oxyhæmoglobin into a globulin, which may be absorbed, and hæmatin, which passes into the feces. Hæmoglobin is without doubt formed in the body from simple proteids by a synthetic process. (for further information see pp. 529 and 574, and likewise under the section on Blood.)

(O)-Hæmoglobin (see p. 517).

NO-Hæmoglobin (see p. 512).

**Methæmoglobin.**—This is found in blood-stains, and may be considered as oxyhæmoglobin which has undergone a chemical change whereby some of the loosely combined oxygen has been liberated.<sup>3</sup>

**Hæmatin**,  $C_{37}H_{32}N_4O_4Fe$ .—This is a cleavage-product of hæmoglobin in the presence of oxygen. (See above, under Hæmoglobin). It is not itself a constituent of the body. It is insoluble in dilute acids, alcohol, ether, or chloroform, but is soluble in alkalies or in acidified alcohol or ether, showing characteristic absorption-bands. If a little dry blood be placed on a microscope slide with NaCl and moistened with glacial acetic acid, and warmed, characteristic brown microscopic crystals of *harmin*,  $C_{37}H_{32}N_4FeO_5 \cdot HCl$ , crystallize out. If these crystals and the spectroscopic test be obtained, one can be absolutely positive of the presence of blood.

**Hæmochromogen**,  $C_{64}H_{64}N_8Fe_2O_7$ .—This substance has the same composition as hæmatin, only it contains less oxygen.<sup>4</sup> If reduced hæmoglobin be heated in sealed tubes with dilute acids or alkali in absence of oxygen, a purple-red compound is produced called

<sup>1</sup> Herter and Wakeman: *Journal of Experimental Medicine*, 1899, vol. iv. p. 307.

<sup>2</sup> Read Stewart, G. N.: *Journal of Physiology*, 1899, vol. xxiv. p. 238.

<sup>3</sup> Zeynek: *Archiv für Physiologie*, 1899, S. 460.

<sup>4</sup> Zeynek: *Zeitschrift für physiologische Chemie*, 1898, Bd. 25, S. 492.



hæmochromogen, which is a crystallizable cleavage-product of hæmoglobin. According to Hoppe-Seyler the oxygen in oxyhæmoglobin is bound to the hæmochromogen group. Hæmochromogen treated with a strong dehydrating agent is converted, with elimination of iron, into *hæmatoporphyrin*,  $C_{16}H_{18}N_4O_3$ , an isomer of bilirubin. Hæmatoporphyrin is said to occur in normal urine.<sup>1</sup> Hæmatoporphyrin treated with nascent hydrogen is converted into a body believed to be identical with hydro- or urobilirubin. Analogous to this is the work of the liver in the body, manufacturing the biliary coloring matter from hæmoglobin, and retaining the separated iron for the synthesis of fresh hæmoglobin (see p. 529). *Hæmatoidin*, found in old blood-stains, is believed to be identical with bilirubin.

**The Bile-pigments.**—The ordinary coloring matter of yellow human bile is *bilirubin*,  $C_{32}H_{34}N_4O_6$ . The next higher oxidation-product is the green *biliverdin*,  $C_{32}H_{26}N_4O_6$ , which is the usual dominant color in the bile of herbivora. These coloring-matters and others derived from them have been found in gall-stones. Jolles<sup>2</sup> gives the following products of the oxidation of bilirubin:

Bilirubin (red)	$C_{32}H_{34}N_4O_6$
Biliverdin (green)	$C_{32}H_{26}N_4O_6$
Bilicyanin (blue)	?
—— (violet)	?
—— (red)	?
—— (brown)	?
Bilixanthin (brownish-yellow)	$C_{32}H_{18}N_4O_6$

If nitric acid containing a little nitrous acid be added to a solution of bilirubin, a play of colors is observed at the juncture of the two fluids, undoubtedly depending upon various stages of oxidation. Above is a ring of green (biliverdin), then blue and violet (bilicyanin), red, yellowish-brown (bilixanthin). Bilixanthin (= choletelin) is the highest oxidation-product. The above is known as *Gmelin's test*.<sup>3</sup>

If bilirubin or biliverdin is subjected to the action either of nascent hydrogen or of putrefaction it is reduced to hydrobilirubin,  $C_{32}H_{44}N_4O_7$ . This substance is therefore formed in the intestinal tract, is in part absorbed, and appears in the urine, where it is called urobilin, though the two are identical. Urobilin gives a yellowish coloration to the urine. Injection into the blood-vessels of distilled water, ether, chloroform, the biliary salts, or arsenuretted hydrogen, produces a solution of the red blood-corpuscles and conversion of hæmoglobin into biliary coloring matters which are thrown out in the urine. Bilirubin, biliverdin, and bilicyanin give characteristic spectra.

**Melanins.**—Under this name are classed the pigments of the skin, of the retina, and of the iris. In melanosis and kindred diseases they are deposited in black granules. Abel and Davis<sup>4</sup> prepared pure pigment from the skin of the negro and find that it contains no iron and 1.5 per cent. of sulphur. These pigments arise from proteid. On decomposition they yield two melaninic acids.<sup>5</sup>

**Tryptophan.**—This is said to be a cleavage-product of hemipeptone in tryptic digestion;<sup>6</sup> it gives a red color with chlorine and a violet color with bromine, due to halogen-addition compounds.

**Lipochromes.**—These include *lutein*, the yellow pigment of the corpus luteum, of

<sup>1</sup> Garrod: *Journal of Physiology*, 1894, vol. 17, p. 348.

<sup>2</sup> *Pflüger's Archiv*, 1899, Bd. 75, S. 446.

<sup>3</sup> For a delicate modification of this test see Jolles: *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, S. 461.

<sup>4</sup> *Journal of Experimental Medicine*, 1896, vol. i, p. 361.

<sup>5</sup> Jones: *American Journal of Physiology*, 1899, vol. ii, p. 380.

<sup>6</sup> Stadelmann: *Zeitschrift für Biologie*, 1890, Bd. 26, S. 491.

blood-plasma, butter, egg-yolk, and of fat; likewise *visual purple* of the retina, which is bleached by light. Solutions of the pure visual purple from rabbits or dogs become clear as water on exposure to light.<sup>1</sup>

#### CHOLESTERIN.

**Cholesterin**,  $C_{27}H_{45}OH$ .—This is found in all animal and vegetable cells and in the milk.<sup>2</sup> It is especially present in nervous tissue and in blood-corpuscles. It is excreted through the bile and through the intestinal wall.<sup>3</sup> In the blood-plasma it is present as an ester combined with oleic and palmitic acids, while in the corpuscle it occurs as simple cholesterin.<sup>4</sup> It may be prepared by dissolving gall-stones in hot alcohol, from which solution the cholesterin crystallizes on cooling in characteristic plates. It is insoluble in water or acids, but soluble in the biliary salts, ether, and hot alcohol. It is probably not absorbed by the intestinal canal. In human feces stercorin appears instead of cholesterin.<sup>5</sup> This stercorin (the koprosterin of Bondzynski) is a dihydrocholesterin,  $C_{27}H_{47}OH$ , and is the result of putrefactive change.<sup>6</sup> Cholesterin feels like a fat to the touch, but is in reality a monatomic alcohol. With concentrated sulphuric acid it yields a hydrocarbon, *cholesterilin*,  $C_{26}H_{42}$ , coloring the sulphuric acid red (Salkowski's reaction). Iso-cholesterin, an isomere, is found combined as an ester with fatty acid in wool-fat or lanolin. The physiological importance of cholesterin is unknown.

#### THE PROTEIDS.

Consideration of the proteids from a purely chemical standpoint is impossible, for their composition is unknown. There exist only the indices of composition furnished by the products of cleavage and disintegration. Bodies at present classed as individuals may sometimes be shown to be identical, with characterizing impurities. It remains for the chemist to do for the proteid group what Emil Fischer with phenyl-hydrazin has accomplished for the sugars.

As a characteristic proteid, egg-albumin may be mentioned. Proteid forms (after water) the largest part of the organized cell, and is found in all the fluids of the body except in urine, sweat, and bile. Proteid contains carbon, hydrogen, nitrogen, oxygen, sulphur, sometimes phosphorus and iron.

**General Reactions.**—A neutral solution of proteid (with the exception of the peptones and proteoses) is partially precipitated on boiling, and is quite completely precipitated on careful addition of an acid (acetic) to the boiling solution. Proteids are precipitated in the cold by nitric and the other common mineral acids, by metaphosphoric but not by orthophosphoric acid. Metallic salts, such as lead acetate, copper sulphate, and mercuric chloride, precipitate proteid; as do ferro- and ferricyanide of potassium in acetic-acid solution. Further, saturation of acid solutions of proteid with neutral salts ( $NaCl$ ,  $Na_2SO_4$ ,  $(NH_4)_2SO_4$ ) precipitates them, as does likewise alcohol in

<sup>1</sup> Kühne: *Zeitschrift für Biologie*, 1895, Bd. 32, S. 26.

<sup>2</sup> Schmidt-Muhlheim: *Pflüger's Archiv*, 1883, Bd. 30, S. 384.

<sup>3</sup> Moraczewski: *Zeitschrift für physiologische Chemie*, 1898, Bd. 25, S. 122.

<sup>4</sup> Hepner: *Pflüger's Archiv*, 1898, Bd. 73, S. 595.

<sup>5</sup> Flint: *American Journal of Medical Sciences*, 1862.

<sup>6</sup> Bondzynski and Hummel: *Zeitschrift für physiologische Chemie*, 1896, Bd. 22, S. 396.

<sup>7</sup> Müller, P.: *Ibid.*, 1900, Bd. 29, S. 129.



neutral or acid solutions. Proteid is also precipitated by tannic acid in acetic-acid solutions, by phospho-tungstic and phospho-molybdic acids in the presence of free mineral acids, by picric acid in solutions acidified by organic acids.<sup>1</sup> The precipitation of proteid is also accomplished by nucleic acid, taurocholic acid, and chondroitic sulphuric acid in acid solutions.

Of the *color-reactions* the action of Millon's reagent has been described (see p. 569). Soluble proteids give the biuret test (see p. 549). With concentrated sulphuric acid and a little cane-sugar a pink color is given when proteid is present (see p. 544). Proteid heated with moderately concentrated nitric acid gives yellow flakes, changing to orange-yellow on addition of alkalis (xantho-proteid reaction). Proteid in a mixture of one part of concentrated sulphuric acid and two parts of glacial acetic acid gives a reddish-violet color (Adamkiewicz), a reaction accelerated by heating. Finally, proteid dissolves after heating with concentrated hydrochloric acid, forming a violet-colored solution (Liebermann).

The following, taken in part from Chittenden,<sup>2</sup> is submitted as a general classification of the proteids:

SIMPLE PROTEIDS.	
<i>Albumins</i>	{ Serum-albumin ;
	{ Egg-albumin ;
	{ Lacto-albumin ;
	{ Myo-albumin.
<i>Globulins</i>	{ Serum-globulin ;
	{ Fibrinogen ;
	{ Myosin ;
	{ Myo-globulin ;
	{ Paramyosinogen ;
<i>Albuminates</i>	{ Cell-globulin.
	{ Acid-albumin ;
	{ Alkali-albumin.
<i>Proteoses and Peptones.</i>	
<i>Coagulated Proteids</i>	{ Fibrin ;
	{ Other coagulated proteids.

COMBINED PROTEIDS.	
<i>Chromo-proteids</i>	{ Hæmoglobin ;
	{ Histo-hæmatins ;
	{ Chlorocruorin ;
	{ Hæmerythrin ;
	{ Hæmocyanin.
<i>Glyco-proteids</i>	{ Mucins ;
	{ Mucoids.

<sup>1</sup> The above list is given by Hammarsten, *Physiological Chemistry*, translated by Mandel, p. 18.

<sup>2</sup> "Digestive Proteolysis," *Curtwright Lectures*, 1895, p. 30.

<i>Nucleo-proteids</i>	{	1. Those yielding para-nuclein	{ Casein ; Pyru ; Vitellin.
		2. Those yielding true nuclein	{ Nucleo-histon ; Cell-nuclein.

*Phospho-glyco-proteids.* Helico-proteid.

#### ALBUMINOIDS.

Collagen (gelatin).

Elastin.

Keratin and Neurokeratin.

**Albumins.**—Bodies of this group are soluble in water and precipitated by boiling, or on standing with alcohol. Serum-albumin is the principal proteid constituent of blood-plasma, while lacto-albumin and myo-albumin are similar bodies found respectively in milk and muscle.

**Globulins.**—These are insoluble in water, but soluble in dilute salt-solutions. They are coagulated on heating. If blood-serum be dialyzed with distilled water to remove the salts present, serum-globulin formerly held in solution separates in flakes. Fibrinogen and serum-globulin are in blood-plasma and the lymph. Myosin is the principal constituent of dead muscles; in the living muscle myosin is said to be present in the form of myosinogen. Myoglobulin in muscle is akin to serum-globulin in plasma. Paramyosinogen in muscle is characterized by the low temperature at which it coagulates ( $+47^{\circ}$ ). Cell-globulin is also found in the animal cell.

The globulins of vegetable cells are interesting as having been obtained in well-defined crystalline form and in great purity of composition.<sup>1</sup> These are not generally coagulable by heat, and indeed vegetable proteids show many points of divergence from those of the animal.

Osborne<sup>2</sup> finds that solutions of pure crystalline edestine obtained from plants take up hydrochloric acid in exact chemical relations, forming the hydrochlorate or bishydrochlorate of edestine. The simplest formula for edestine (containing two atoms of sulphur) which can be calculated gives a molecular weight of 7,138, twice which is 14,276. This latter molecular weight exactly unites with one molecule of hydrochloric acid to form edestine hydrochlorate. Osborne regards the many variations in similar "native" albumins as being fundamentally caused by the quantity and quality of the acid or alkali with which they unite.

**Albuminates.**—If any of the above native animal proteids or any coagulated proteid be treated with an alkaline solution, alkali albuminate is formed. In this way the alkali of the intestine acts upon proteid. If hydrochloric acid acts on proteid, there is a gelatinization and slow conversion into acid albuminate, a process accelerated by the presence of pepsin. This takes place in the stomach. Both alkali and acid albuminates are insoluble in water, but both are soluble in dilute acid or alkali, without loss of individual identity.

**Proteoses and Peptones.**—These are bodies obtained from the digestion of proteids, through a process of hydrolysis. They are non-coagulable by heat. If a mixture of proteoses and peptones be saturated with ammonium sulphate the proteoses are said to be precipitated, while true peptone remains in solution. The chemical identity of this true peptone is still, however, to be established. In the gastric digestion of fibrin, proto-peptose, hetero-peptose, and deutero-peptose B. arise as primary cleavage products.<sup>3</sup>

<sup>1</sup> Osborne : *Journal of American Chemical Society*, 1894, vol. xvi., Nos. 9, 10; and other articles in the same journal by the same author.

<sup>2</sup> *Op. cit.*, 1899, vol. 21, p. 486.

<sup>3</sup> Zuntz, E. : *Zeitschrift für physiologische Chemie*, 1899, Bd. 28, S. 132.



Fibrin yields a carbohydrate radicle which appears in deutero-proteose B and subsequently in peptone A.<sup>1</sup> The primary proteoses are believed to break up into secondary proteoses, such as deutero-proteose A and deutero-proteose C, and perhaps others, and these secondary proteoses may be converted into peptones, although gastric digestion will not convert some deutero-proteoses into peptone.<sup>2</sup> Egg albumin and other proteids yield similar products. The whole process of proteolytic cleavage has been compared with the hydrolytic cleavage of starch into dextrins and sugars. According to Kuhne, proteid consists of a hemi- and an anti- group, which separate into distinct hemi- and anti- bodies in proteolysis. Of the final products, hemi- and anti-peptone, only the former yields leucin and tyrosin in tryptic proteolysis. This is the only radical difference between the two peptones, hence hemi-peptone has never been isolated. Kutscher<sup>3</sup> denies the existence of anti-peptone and shows that prolonged tryptic proteolysis almost completely transforms proteid into amido bodies.

**Coagulated Proteids.**—These are insoluble in water, salt-solutions, alcohol, dilute acids and alkalis, but soluble in strong acids and alkalies, pepsin-hydrochloric acid, and alkaline solutions of trypsin. The chemical or physical change which is effected in coagulation of proteid is unknown.

**Combined Proteids.**—These consist of proteid united to non-proteid bodies such as hæmochromogen, carbohydrates, and nucleic acid.

**Chromo-proteids.**—These are compounds of proteid with an iron- or copper-containing pigment, like hæmoglobin, which has already been described. *Histohæmatins* are iron-containing pigments found especially in muscle. That which is found in muscle is called myohæmatin, and resembles hæmochromogen somewhat in its spectroscopic appearance, and is believed to be present in two forms corresponding to hæmoglobin and oxyhæmoglobin. It has been regarded as an oxygen-carrier to the tissues. Among the invertebrates the blood often contains only white corpuscles with sometimes a colored plasma. Thus the blood-serum of the common earth worm contains dissolved hæmoglobin, that of some other invertebrates a green respiratory pigment, *chlorocruorin*, whose characterizing component seems similar to hæmatin: *hæmerythrin* occurs in the pinkish corpuscles of *Sipunculus*, while the blood of crabs, snails, and other animals (mollusks and arthropods) is colored blue by a pigment, *hæmocyanin*, which contains copper instead of iron.

**Glyco-proteids.**—These consist of proteids combined with a carbohydrate. They are insoluble in water, but soluble in very weak alkalis. On boiling with dilute mineral acids they yield a reducing substance.

**Mucins** are found in mucous glands, goblet cells, in the cement substance of epithelium and in the connective tissues. Of the nearly related mucoids may be named *colloid*, a substance appearing like a gelatinous glue in certain tumors; *pseudo-mucoid*, the slimy body which gives its character to the liquid in ovarian cysts; and *chondro-mucoid*, found as a constituent of cartilage. On boiling chondro-mucoid with dilute sulphuric acid it yields acid-albuminate, a peptone substance, and chondroitie acid. The last is a nitrogenous ethereal sulphuric acid, yielding a carbohydrate on decomposition, and found preformed in every cartilage<sup>4</sup> and in the amyloid liver.<sup>5</sup> It is, of course, not a proteid. Amyloid is similar to chondro-mucoid, and may be identical with it. It is said to consist of chondroitie sulphuric acid in combination with proteid,<sup>6</sup> and yields proteid and phosphoric acid on decomposition.

<sup>1</sup> Pick: *Zeitschrift für physiologische Chemie*, 1899, Bd. 28, S. 219.

<sup>2</sup> Folin: *Ibid.*, 1898, Bd. 25, S. 152.

<sup>3</sup> *Die Endprodukte der Trypsinverdauung*, Strassburg, 1899.

<sup>4</sup> Mörner: *Zeitschrift für physiologische Chemie*, 1895, Bd. 20, S. 357.

<sup>5</sup> Oddi: *Archiv für exper. Pathologie und Pharmacologie*, 1894, Bd. 33, S. 376.

<sup>6</sup> Krawkow: *Ibid.*, 1897, Bd. 40, S. 195.

**Nucleo-proteids, or Nucleo-albumins<sup>1</sup> and Nucleic Acids.**—These are compounds of proteid with nuclein, which latter yields phosphoric acid on decomposition. If nucleo-proteid, which is found in every cell, be digested with pepsin-hydrochloric acid, there remains a residue of insoluble nuclein, which is likewise insoluble in water but soluble in alkalies. If this nuclein yields xanthin bases on further decomposition, it is called true nuclein; if it fails to yield these bases, it is called paranuclein or pseudonuclein. Nucleo-proteids yielding proteid and paranuclein on decomposition include the casein of milk, pyin of the pleural cavity, vitellin of the egg, Bunge's iron-containing hæmatogen of the egg, as well as nucleo-proteids found in all protoplasm. They all contain iron. Paranuclein is probably absorbable (see p. 514). Casein yields on peptic digestion phosphorized albumoses from which paranuclein is split: this cleavage is followed by the further digestion of the albumose and the gradual solution of the paranuclein.<sup>2</sup> Kobrak<sup>3</sup> shows that woman's casein has two-thirds the acidity of cow's casein, but that the former dissolved and reprecipitated six times has the same properties as the latter. He believes that woman's casein may consist of cow's casein united with another product of more basic properties.

A second group of nucleo-proteids yields true nuclein on decomposition. This true nuclein is a modified form of the original nucleo-proteid, and consists of nucleic acid in combination with proteid. On decomposition the nuclein breaks up into its constituent proteid and nucleic acid, which latter always yields one or more of the xanthin bases, which are, therefore, called nuclein bases. The nucleic acid is similar to that derived from sperm, which is combined with protamin in the sperm nucleus. The nucleic acid of yeast nuclein yields guanin and adenin, that of a bull's testicle adenin, hypoxanthin, and xanthin, that of the thymus adenin and guanin, that of the pancreas guanin alone. The latter has been termed "guanylic acid," and "adenylic" and "xanthylic" acids may also be considered individual nucleic acids. Each one of this family of acids has the power of combining with any soluble proteid to form nucleo-proteid, hence there may exist a large variety of nucleo-proteids. And the variety is further increased by the diversity of other decomposition products yielded by the various nucleic acids. Thus most nucleic acids yield thymic acid, which, however, cannot be found in pancreas nucleo-proteid. A crystalline base called cytosin has been discovered in thymus nucleic acid. Some nucleic acids, like that derived from yeast, readily yield carbohydrates (a hexose and a pentose), while others, like thymus nucleic acid, show the presence of the carbohydrate group only in the production of levulinic acid after very thorough decomposition; and still others (salmon sperm) fail to indicate the presence of any carbohydrate radicle. According to Kossel, nuclei may at times contain free nucleic acid. According to Bang,<sup>4</sup> nucleic acid may unite in three ways: with protamin, as in sperm nucleic acid; loosely with proteid, as in most nucleo-proteids; and strongly with proteid, as in pancreas nucleo-proteid. The last-named pancreas nucleic acid yields guanin on decomposition, and has been termed "guanylic acid." Bang gives the following analysis: guanin, 35 per cent. (containing nine-tenths of all the nitrogen present); a little ammonia; a pentose, 30 per cent., and  $P_2O_5$ , 17.6 per cent. The rest unaccounted for is 17.5 per cent.

**Phospho-glyco-proteids.**—This class is represented by Hammarsten's *holico-proteid*, which yields paranuclein, and, unlike other nucleo-proteids of the paranuclein class, it yields a reducing carbohydrate on boiling with acids.

**The Albuminoids.**—These are bodies derived from true proteid in the body, but not themselves convertible into proteid. They are resistant to the ordinary proteid solvents, and as a rule exist in the solid state when in the body.

<sup>1</sup> These two terms are used here as synonymous, though Hammarsten would confine the term nucleo-albumin to those proteids which yield paranuclein.

<sup>2</sup> Salkowski: *Zeitschrift für physiologische Chemie*, 1899, Bd. 27, S. 297.

<sup>3</sup> *Pflüger's Archiv*, 1900, Bd. 80, S. 69.

<sup>4</sup> *Zeitschrift für physiologische Chemie*, 1898, Bd. 26, S. 133.



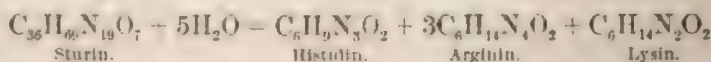
**Collagen.**—This is the chief constituent of the fibres of connective tissue, of the organic matter of bone (ossein) and is likewise one of the constituents of cartilage. Collagen is insoluble in water, dilute acids and alkalis. On boiling with water it forms *gelatin* through hydration, which is soluble in hot water, but gelatinizes on cooling (as in bouillon). Dry gelatin swells when brought into cold water. By continuous boiling or by gastric or tryptic digestion further hydration takes place with the formation of soluble gelatin peptone. Gelatin fed will not take the place of proteid, but, like sugar, only more effectively, it may prevent proteid waste by being burned in its stead.<sup>1</sup> Gelatin yields leucin and glycocoll on decomposition, but no tyrosin. It therefore gives the biuret reaction, but none with Millon's reagent. It contains but little sulphur. It yields about the same amido-acids as ordinary proteid.

**Elastin.**—This is very insoluble in almost all reagents and in boiling water. On decomposition it yields leucin, tyrosin, glycocoll, and lysatin. It is slowly hydrated by boiling with dilute acids, and by pepsin hydrochloric acid. It contains very little sulphur, and gives Millon's test. It is found in various connective tissues, and especially in the cervical ligament.

**Keratin and Neuro-keratin.**—These are insoluble in water, dilute acids and alkalis; insoluble in pepsin hydrochloric acid, and alkaline solutions of trypsin. Keratin is found in all horny structures, in epidermis, hair, wool, nails, hoofs, horn, feathers, tortoise-shell, whalebone, etc. Neuro-keratin has been discovered in the brain, and in the medullary sheath of nerve-fibres.<sup>2</sup> On decomposition with hydrochloric acid keratin yields all the products given by simple proteids. It contains more sulphur than simple proteid and yields more tyrosin. Drechsel<sup>3</sup> believes that it is transformed from simple proteid by the substitution of sulphur for some of the oxygen and of tyrosin for leucin or other amido-acid. Part of the sulphur is loosely combined, and a lead comb turns hair black, due to the formation of lead sulphide. There are different keratins, and their sulphur content varies greatly.

**Histon.**—Histon is a proteid split off from yeast nuclein and the nuclein of the white blood-corpuscles and blood plates. Kossel has suggested that it is a combination of proteid and protamin, which the investigations of Bang<sup>4</sup> tend to confirm.

**Protamins and Remarks on the Theoretical Composition of the Proteid Molecule.**—The protamins have been discovered in fish-sperm united with nucleic acid. According to Kossel, protamins are the simplest proteids. They all give the biuret test. On heating with dilute acid or in tryptic digestion they are converted into protone (protamin peptone), and then they break up into amido acids. Several protamins have been discovered. That obtained from sturgeon-sperm is called sturin, from the herring, clupein, from the salmon, salmin, and from the mackerel, scombrin. Sturin, according to Kossel,<sup>5</sup> breaks up as follows:



Kossel's investigations show that salmin and clupein are identical and yield on decomposition arginin and amido valerianic acid, while scombrin also yields arginin, without any histidin or lysin.<sup>6</sup>

<sup>1</sup> Voit: *Zeitschrift für Biologie*, 1872, Bd. 8, S. 297.

<sup>2</sup> Kühne and Chittenden: *Ibid.*, 1890, Bd. 26, S. 291.

<sup>3</sup> Ladenburg's *Handwörterbuch der Chemie*, 1885, Bd. 3 S. 571.

<sup>4</sup> *Zeitschrift für physiologische Chemie*, 1899, Bd. 27, S. 463.

<sup>5</sup> *Deutsche medizinische Wochenschrift*, 1898, No. 37.

<sup>6</sup> *Zeitschrift für physiologische Chemie*, 1899, Bd. 26, S. 588.

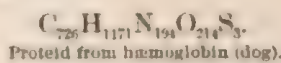
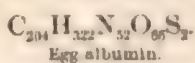
All proteids yield histidin, arginin, and lysin on decomposition. As regards the composition of the proteid molecule, Kossel pictures a protamin nucleus like sturin, to which may be attached leucin, tyrosin, glucosamin, or glycecoll, and to these again sulphur, iodine, or iron. Treatment of proteid with 20 per cent. hydrochloric acid or tryptic digestion may break it up into leucin, tyrosin, histidin, argenin, lysin, etc. Kossel speaks of histidin, arginin, and lysin as hexon-bases, since they (and leucin also) contain six atoms of carbon, and he calls attention to the fact that in this respect they are similar to the carbohydrates. Just as carbohydrates exist as poly-hexoses, so protamins and proteids may be built up as poly-hexon-bases. Cohn has found that proteid may yield as much as 50 per cent. of leucin.

The products derived from proteid in metabolism are different from the above. Thus it has been found that the body's proteid, the proteid from meat, and gelatin, may all yield about 60 per cent. of dextrose in diabetes.<sup>1</sup> It has been further shown<sup>2</sup> that the metabolism of the body's proteid, of casein, and of gelatin yields between 3 and 4 per cent. of glycecoll, which may be eliminated as hippuric acid. It is possible to conceive of a carbohydrate portion united to a protamin nucleus and to amido bodies such as glycecoll<sup>3</sup> (see p. 558).

Müller and Seeman<sup>4</sup> have declared that the source of the sugar in diabetes must be the hexon-bases and leucin, but Halsey<sup>5</sup> has shown that feeding leucin will not increase the sugar in diabetes. Halsey suggests a synthetic formation of sugar from lower proteid decomposition-products, but a synthetic formation of sugar in the animal has never been shown. It must be admitted that we are still in the dark regarding even the simplest expression of the constitution of proteid.

It has been impossible within the limits set to do more than to glance at the proteid bodies. Many facts concerning the behavior of proteids have been mentioned throughout the text, and cannot be classified here.

The size of the proteid molecule must be very great, and one computation shows the following figures<sup>6</sup> (see also p. 577):



It is well, perhaps, finally, to speak of experiments which, however incomplete, at least throw some light on the possibilities of the problem of the synthesis of proteid. Lilienfeld<sup>7</sup> through the condensation of the ethyl-ester of

<sup>1</sup> Reilly, Nolan, and Lusk: *American Journal of Physiology*, 1898, vol. i. p. 395.

<sup>2</sup> Parker and Lusk: *Ibid.*, 1900, vol. iii. p. 472.

<sup>3</sup> Ray, McDermott, and Lusk: *Ibid.*, 1899, vol. iii. p. 153.

<sup>4</sup> *Deutsche medicinische Wochenschrift*, 1899, S. 209.

<sup>5</sup> *Sitzungsberichte der Gesellschaft zur Beförderung der gesammten Naturwissenschaften, zu Marburg*, 1899, S. 102.

<sup>6</sup> Bunge: *Physiologische Chemie*, 3d ed., 1893, S. 56.

<sup>7</sup> *Verhandlungen der Berliner physiologischen Gesellschaft, Archiv für Physiologie*, 1894, S. 383.



glycocoll has obtained a body insoluble in water, but swelling in it, forming a gelatinous mass. The substance gives the biuret reaction, is insoluble in alcohol and dilute hydrochloric acid, but dissolves in pepsin-hydrochloric acid. These reactions show its kinship to gelatin. Lilienfeld likewise describes a synthetically formed peptone and a coagulable proteid,<sup>1</sup> the peptone formed principally through condensation of the above-described product with the ethyl-esters of the amido- bodies, leucin and tyrosin, the proteid from the same with addition of formic aldehyde. Grimaux likewise has produced, with other reagents, colloids which resemble proteids. Probably none of these substances are native proteids, but they furnish indications of lines of attack for the future mastery which in time is sure.

<sup>1</sup> Verhandlungen der Berliner physiologischen Gesellschaft, *Archiv für Physiologie*, 1894, S. 555.

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